Pulmonary rehabilitation in patients with severe chronic obstructive pulmonary disease

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Contents

CHAPTER 1

General introduction and aims of the study

1.1 Chronic Obstructive Pulmonary Disease (COPD): definition, causes and consequences

Chronic Obstructive Pulmonary Disease (COPD) is characterized by chronic airflow obstruction and includes patients with chronic obstructive bronchitis and emphysema [1] Chronic bronchitis is accompanied by inflammation, narrowing and fibrosis of the peripheral airways, and goblet cell metaplasia Emphysema is characterized by abnormal enlargement of the alveolar spaces, reduced elastic recoil and destruction of the alveolar walls [2]

COPD primarily affects middle-age and older persons and is associated with increased morbidity and mortality rates The prevalence of severe asthma and COPD in the Netherlands has increased from 2 to 4% during the last 15 years and is still increasing [3] The most frequent cause of COPD is smoking Additional risk factors are poorly controlled asthma in the past, socioeconomic status, and hereditary factors Deficiency of the protein α_1- antitrypsin predisposes to the development of emphysema at an early age, which is accelerated by smoking [4]

Most patients experience dyspnoea on exertion or at rest Complaints of wheezing, cough and sputum production are variable The ventilatory impairment and the sensation of dyspnoea limit exercise tolerance and result in deconditioning [5]

The increased airway resistance and the loss of elastic recoil are accompanied with a reduced ventilatory capacity and an increased work of breathing Ventilation to perfusion inhomogeneity and a reduced diffusion capacity lead to disturbances in gas exchange and increase the ventilatory requirement [6] Hyperinflation shifts the diaphragm to an unfavourable position on its length tension relationship [7] As a result inspiratory muscle strength and endurance are reduced [8] Hypoxaemia, hypercapnia, inactivity, malnutrition and treatment with corticosteroids may further impair respiratory and peripheral muscle function [9-11]

COPD is a progressively disabling disease which results in impaired physical and psychosocial functioning In patients suffering from COPD, the prevalence of depression and anxiety is high Consequently, health-related quality of life and well-being in these patients is commonly reduced [12]

1.2 Exercise limitation in COPD

Exercise tests can be used to assess the factors limiting exercise tolerance, to quantify the extent of disability and to set goals for exercise training

The mechanisms involved in the exercise limitation in patients with COPD can be evaluated during a maximal incremental exercise test on a cycle ergometer or on a treadmill The power plant model in Figure 1 1 illustrates the physiological systems involved in the gas transport from the lungs to the working muscles and

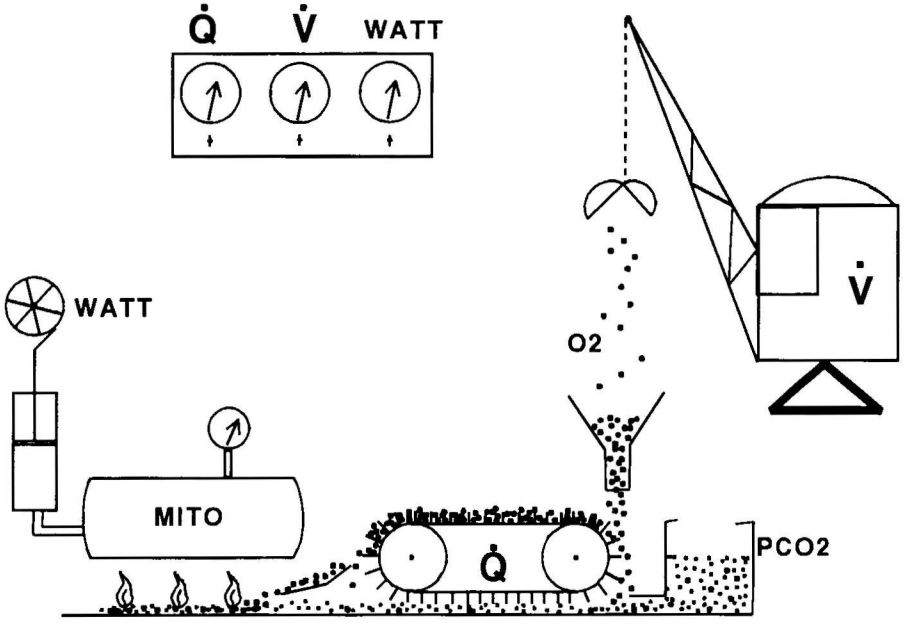

Figure 1.1

vice versa. The crane, representing the lungs, delivers the coal (oxygen) via a funnel (diffusion capacity of the alveolar-capillary membrane) on the conveyer belt (cardiocirculatory system), which transports the fuel to the compartment where the combustion takes place (mitochondria of the working muscles). The power output depends on the efficiency of the engine and the generator. The waste products (CO_2) together with the spilled fuel are transported by the conveyer belt to the bunker (central venous blood), from which they are removed (expired) by the crane. The process is regulated by a controlling system (central nervous system), which receives incoming signals from the various compartments of the power plant. The factors contributing to the exercise limitation in COPD are shown in Table 1.1 and will be discussed below.

Metabolic and cardiocirculatory limitation

Generally, patients with light to moderate COPD ($FEV_1 \geq 1.5$ L or 60% of predicted) are, similar to normal subjects, limited during exercise by the cardiocirculatory system and by metabolic factors on the level of the peripheral muscles. This is reflected by the conveyor belt of the power plant model. The transport capacity of the belt depends on its speed (cardiac output) and the height of the compartments on the belt (haemoglobin concentration of the blood). During pro-

gressive exercise, patients with mild and moderate COPD may achieve their age specific maximal heart rate, and blood lactate may increase (base excess decreases) by more than 10 mmol/L [13] In these patients, both perceived leg effort and dyspnoea contribute to the subjective exercise limitation [14]

Ventilatory limitation

Patients with moderate to severe COPD ($FEV_1 \leq 1.5$ L or 60% of predicted) are ventilatory limited during exercise due to the abnormal respiratory mechanics and gas exchange disturbances This is reflected by a decreased capacity of the crane and a narrowed opening of the bunker in the power plant model Failure of the respiratory pump results in an insufficient elimination of carbon dioxide and, hence, hypercapnia FEV_1, diffusion capacity and respiratory muscle function have been identified as important determinants of exercise capacity [15,16] Dynamic hyperinflation during exercise due to insufficient time for expiration and increased breathing frequency will increase the ventilatory load and will further compromise ventilatory muscle function [17] Dynamic hyperinflation will result in neuroventilatory dissociation, a disproportionate rise in inspiratory effort in relation to flow, which is an important determinant of breathlessness [18]

At peak exercise, these patients are limited by dyspnoea, although leg fatigue may also play a role [19] At that point, maximum minute ventilation approaches or exceeds predicted maximal exercise ventilation or maximal breathing capacity (low or negative breathing reserve) in many patients However, dyspnoea may limit exercise performance before predicted maximal ventilation is reached [18] As a result, predicted maximal heart rate may not be reached Improvement in the ventilation to perfusion ratio (optimalizing the position of the funnel above the conveyor belt) may prevent a concomitant fall in PaO_2 [5] The ventilatory muscle load can be assessed by measuring oesophageal pressure swings and quantified by calculation of the tension time index (TTI) [20] A TTI value exceeding 0.15 is indicative of respiratory muscle fatigue [21]

Limitation in oxygen-uptake and transport

In patients with severe COPD, hypoxaemia may occur during exercise due to a limitation in oxygen-uptake and transport capacity This is caused by a reduced pulmonary vascular bed and gas exchange surface area (diffusion capacity), a reduced contact-time, ventilation to perfusion inhomogeneity, and a reduced cardiac output resulting in a low mixed venous PO_2 As a result the gap between the alveolar and arterial oxygen tension [$P(A\text{-}a)O_2$] widens [6] In contrast, hypoxaemia due to alveolar hypoventilation has no effect on $P(A\text{-}a)O_2$ In normal subjects, $P(A\text{-}a)O_2$ may rise from 1.5 kPa at rest up to 3 kPa during exercise at high levels of VO_2 up to 3 L/min depending on the age of the subject [22] Thus, an increase in $P(A\text{-}a)O_2$ by more than 2 kPa in patients with COPD at lower work rates suggests a diffusion-perfusion limitation or impaired cardiac function

Table 1 1 ADL activities of daily life, COPD chronic obstructive pulmonary disease, HR heart rate, MPAP mean pulmonary artery pressure, MVV maximal voluntary ventilation, $P(A\text{-}a)O_2$ alveolar-arterial difference in oxygen tension, $PaCO_2$ arterial carbon dioxide tension, PaO_2 arterial oxygen tension, PVR pulmonary vascular resistance, RV right ventricle, RVEF right ventricular ejection fraction, TTI tension time index, VE minute ventilation

COPD	Exercise Limitation	Training Method	Effect
mild	**metabolic-cardiocirculatory limitation** *measurements at maximum exercise* HR ≥ 220 – age lactate > 10 mmol/L base excess decrease > 10 mmol/L perceived exertion general (leg) fatigue, dyspnoea	endurance training breathing exercises	improved aerobic capacity reduced lactate at identical work loads
moderate	**ventilatory limitation** limited ventilatory capacity respiratory muscle weakness and fatigability impaired alveolar gas exchange *measurements at maximum exercise* VEmax > 70% of MVV or VEmax predicted tension time index (TTI) > 0 15 $PaCO_2$ ↑, PaO_2↓ perceived exertion dyspnoea	interval training inspiratory muscle training isolated muscle training upper extremity training training of ADL breathing exercises ergonomics nutritional support anabolic steroids	reduced lactate and ventilation at identical work loads improved muscular efficiency and coordination increased respiratory muscle strength and endurance improved performance of daily life activities reduced dyspnoea

Table 1.1 continuation

COPD	Exercise Limitation	Training Method	Effect
	limitation in oxygen-uptake and transport		
	diffusion limitation		
	shunt		
	ventilation/perfusion inequality		
	reduced cardiac output		
		supplemental oxygen during	*improved exercise performance*
	measurements at maximum exercise	**exercise training**	*(uncontrolled studies)*
	$P(A\text{-}a)O_2$ ↑		
	PaO_2 ↓		
	mixed venous PO_2 ↓		
severe	perceived exertion dyspnoea	**eccentric exercise training**	*unknown*
	impaired pulmonary haemodynamics		
	increased afterload		
	impaired right ventricular performance		
	measurements at maximum exercise		
	PVR ↑		
	MPAP ↑		
	RVEF ↓, RV stroke volume ↓		
	limitation in peripheral muscle function		
	reduced muscle strength and endurance		

In patients with COPD, pulmonary vascular resistance and pulmonary artery pressure rise during exercise Hypoxaemia will worsen pulmonary haemodynamics due to hypoxic pulmonary vasoconstriction and further increases the load placed on the right ventricle.[23,24] In some patients, left ventricular function may be impaired as well [25]

Limitation in peripheral muscle function

Recent studies have shown that peripheral muscle dysfunction may contribute to the exercise limitation in patients with COPD [16] Deconditioning of the skeletal muscles is attributed to inactivity, corticosteroids, hypoxaemia and impaired nutritional state [11,25,27] A reduced oxidative capacity of the skeletal muscles has been found, which results in early onset lactic acidosis during exercise [28,29] Studies in normal subjects under hypoxic conditions have suggested a diffusion barrier at the level of the peripheral muscles Muscle diffusion capacity was reduced especially in deconditioned muscles, thus limitating oxygen delivery and utilization [30]

Conclusion

The mechanisms involved in exercise limitation in patients with moderate to severe COPD are complex and interrelated The factors limiting exercise performance are not strictly related to respiratory function. Hence, the exercise response will vary widely between subjects and depends on respiratory mechanics, gas exchange, ventilatory muscle function, pulmonary vascular disease, physical fitness, nutritional state, dyspnoea sensation and motivation Therefore, the exercise limitation has to be evaluated in every patient before exercise training can be prescribed

Exercise tests at constant (submaximal) work loads are used to measure endurance and may reflect activities of daily life The performance during these tests depend on exercise intensity and may be influenced by the same factors which limit maximum exercise capacity Moreover, endurance exercise capacity is highly dependent on motivational factors Therefore, exercise limiting factors should be assessed in each individual patient with COPD.

1.3 Pulmonary rehabilitation

Pulmonary rehabilitation is indicated in patients who experience handicaps as a result from their ventilatory impairment and disabilities [31] Pulmonary rehabilitation has been defined as "a multidimensional continuum of services directed to persons with pulmonary disease and their families, usually by an interdisciplinary team of specialists, with the goal of achieving and maintaining the individual's maximum level of independence and functioning in the community" [32] The goals of pulmonary rehabilitation are achieved by an accurate diagnosis and evaluation of exercise

limitation, optimalizing medical treatment, exercise training, physical therapy, breathing retraining, nutritional advice, education and psycho-social support [1 31 33 34] In the Netherlands, guidelines for the assessment of candidates and goals of the treatment have recently been published [35] The benefits of pulmonary rehabilitation in patients with COPD have been well established [33 36 37]

Pulmonary rehabilitation in patients with COPD as carried out in our clinic comprises initial assessment, intervention and follow-up Intervention consists of a comprehensive in-patient programme for 10 weeks, 5 days/week The interdisciplinary team comprises a physician, a pulmonary physiologist, nurse, physical therapist, exercise therapist, dietician, social worker, psychologist and art therapist The partner and close relatives are involved in the treatment as much as possible

During their stay, the patients learn to manage daily household tasks such as making their own bed, preparing meals, and washing the dishes Plans are worked-out to continue exercises at home and to participate in maintenance exercise groups and in recreational activities after discharge Patients who need home care are referred to primary health care services Evaluation takes place during an out-patient visit approximately two months after completion of the programme The exercise training programme is discussed in more detail in Chapter 3

1.3.1 Exercise training in patients with COPD

Exercise training is a key component of pulmonary rehabilitation The training regimen has to be individually based, taken into consideration severity of the disease and exercise limitation [38] Many training regimens varying in exercise mode, frequency, intensity and duration have been shown beneficial effects on functional capacity [39]

The effects of different training methods in patients with COPD are summarized in Table 1 1 In patients with light to moderate COPD, endurance strength training may improve cardiorespiratory fitness and aerobic capacity similar to normal subjects [36] A physiologic training response in terms of proportionally reduced minute ventilation (VE) and lactate levels at iso work rates has been observed in patients with moderate COPD The effect was more pronounced if training was performed above the anaerobic threshold [40]

Recently, similar training effects have been found in patients with severe COPD after endurance training at moderate work rates [41] However, many patients with severe COPD do not tolerate exercise intensities which result in a physiologic training effect In these patients, training may improve exercise efficiency (work load/VO_2) and coordination, and may reduce dyspnoea on exertion Beneficial effects of training has been observed on maximal work load, endurance exercise capacity, walking distance, perceived breathlessness and quality of life[42 50] In patients with respiratory muscle weakness, inspiratory muscle training may increase ventilatory muscle strength and endurance and may improve exercise performance[37 51] and nocturnal oxygen saturation[52]

In patients with severe COPD and a peak VO_2 of less than 1 L/min, training modalities directed towards higher exercise intensities may result in a greater training response than endurance training at low exercise intensities [39 53] Higher exercise intensities may be achieved when exercise is performed for a short duration, at intervals or during training of isolated muscle groups [54] Exercise involving the upper extremities causes dyspnoea at relatively low exercise levels as compared to leg exercise This can be influenced by upper extremity training, as it reduces the ventilatory requirement of arm exercise.[55 56] Nutritional support and anabolic steroids may restore body weight and improve respiratory muscle function in patients with weight loss and muscle wasting [57]

In this study, we focussed on patients with COPD who are hypoxaemic during exercise due to a diffusion-perfusion limitation In these patients, it is necessary to compensate for the insufficient oxygen-uptake during exercise. This can be achieved by supplemental oxygen, which increases the fraction of oxygen in the inspired air. Instead of supplying extra oxygen, exercises demanding small amounts of oxygen may offer an alternative, an example of which is eccentric exercise Eccentric exercise is associated with a reduced oxygen cost and ventilatory requirement, at least in normal subjects. Possibly, it is a valuable type of exercise in patients with COPD.

The literature of oxygen therapy and eccentric exercise is reviewed in the next paragraphs

1.3.2 Oxygen therapy

Patients with COPD and hypoxaemia at rest (PaO_2 < 7.3 kPa) or during sleep may benefit from long-term oxygen therapy.[58 63]

In patients who develop hypoxaemia during exercise, home oxygen therapy may be prescribed if it improves performance of daily life activities.[1] Supplemental oxygen has acute beneficial effects on exercise performance [64 68] In comparison with breathing air, supplemental oxygen has shown to improve endurance work, endurance time for walking and cycling, and six minute walking distance by 20-80%.[64 68] The acute effect was not related to PaO_2 at rest or during exercise. Possible mechanisms are a reduced ventilatory response to exercise[67], ventilatory muscle recruitment[69] and delayed ventilatory muscle fatigue[70 71], improved aerobic capacity of the working muscles[72] and a reduction in breathlessness[68 73]. Supplemental oxygen attenuates the increase in mean pulmonary arterial pressure (MPAP) during exercise, but this effect did not correlate with improvements in exercise performance [68 74]

Recent guidelines recommend the use of supplemental oxygen during training in patients with COPD and exercise-induced hypoxaemia [75] However, the benefits of training with supplemental oxygen in patients with COPD, regardless of PaO_2 at rest or during exercise, have not yet been well established. Uncontrolled studies have reported beneficial effects of oxygen-supplemented exercise training in patients

Table 1.2 Oxygen therapy in COPD

Long-term oxygen therapy in patients with hypoxaemia at rest
– increases life expectancy
– may prevent the development of pulmonary hypertension
– increases quality of life
Supplemental oxygen during exercise
– increases exercise tolerance
– reduces ventilatory response
– ventilatory muscle recruitment
– delays ventilatory muscle fatigue
– increases aerobic capacity
– reduces breathlessness
Supplemental oxygen during exercise training
– improves exercise tolerance (uncontrolled studies)

with COPD.[76,77] In the study by Zack et al.[77], exercise training with supplemental oxygen (4 L/min) increased maximum work load by 14%, while breathing oxygen. Twelve minute walking distance and endurance cycling time increased by more than 50% both on air and oxygen. Degre et al.[76] reported an increase in peak $\dot{V}O_2$ by 10% after training with supplemental oxygen (3-4 L/min), which was related to the PO_2 during exercise. Maximal cardiac output and stroke volume did not change. Recently, no additional effect of training with supplemental oxygen as compared to training on room air has been reported in patients with COPD who did not desaturate during exercise.[78]

The purpose of the present study was to investigate whether supplemental oxygen during the training may enhance the effects of training on room air in patients who develop hypoxaemia during maximal incremental exercise. If supplemental oxygen enables these patients to achieve higher exercise intensities during the training, this treatment might induce an additional physiologic training effect on the cardiocirculatory system and the peripheral muscles in terms of increased oxygen delivery, peripheral oxygen extraction and muscle oxygen utilization.

1.3.3 Eccentric exercise (negative work)

Muscle mechanics and physiological response

Concentric (positive work, Wpos) and eccentric (negative work, Wneg) exercise are different types of dynamic exercise. During Wpos (lifting a weight, walking upstairs) the muscle shortens against an opposing force. Wneg, such as walking downstairs or lowering a weight to the floor, is accomplished by eccentric muscle contractions during which the muscle lengthens in a controlled way.[79]

Table 1.3 Eccentric exercise (negative work) in normal subjects

Eccentric muscle contraction:
- controlled lengthening of the muscle in the direction of an opposing force (gravity)
- requires less ATP and generates a higher maximal muscle force in comparison with concentric muscle contraction

Eccentric exercise in comparison with concentric exercise:
at equal oxygen consumption:
- higher total heat production
- higher heart rate and cardiac output
- higher scores for perceived exertion

at equal work loads:
- lower oxygen consumption
- lower ventilatory requirement
- lower heart rate and exercise ventilation
- lower scores of perceived exertion

Adverse effects:
- temporary and repairable ultrastructural muscle damage
- release of muscle proteins
- delayed-onset muscle soreness

Effects of eccentric exercise training
- increased isometric force
- increased dynamic muscle strength and endurance
- muscle fibre hypertrophy
- adaptation to muscle damage and soreness

Large physiological differences exist between Wpos and Wneg. In frog skeletal muscle, the amount of ATP breakdown during concentric contractions correlated with the amount of (positive) work done by the muscle.[80] In contrast, Curtin and Davies[81] did not find a significant correlation between these parameters during stretching. The tension generated by the cross-bridge linkage of the contractile elements required less ATP during eccentric than during concentric muscle contractions.[81,82]

In healthy subjects, higher forces are generated during Wneg than during Wpos at the same oxygen consumption.[79] The maximal force generated by the arm muscles during Wneg was 14-33% higher.[83] In addition to the metabolic heat produced during exercise, the external energy during Wneg is absorbed by the muscles and converted into heat. As a result, the total heat produced during Wneg may be about 3 times higher than during Wpos at the same oxygen consumption.[84]

At similar work loads, electromyographic activity was reduced during Wneg as compared with Wpos, because fewer motor units were activated [85] In addition, Aura and Komi[86] have shown that the mechanical efficiency during Wneg was positively correlated with work intensity As a result, oxygen consumption, and ventilatory and cardiocirculatory response, as well as the score for perceived exertion is lower during Wneg than during Wpos [79 84 87 92] During steady-state exercise at equal work rates above 100 Watt, heart rate was 30% lower, and VE and VO_2 were 50-70% lower during Wneg than during Wpos. For exercise at similar levels of VO_2 above 1 L/min, heart rate and cardiac output were higher during Wneg [89 91] The score for perceived exertion was 30% lower during Wneg than during Wpos, while for similar levels of VO_2 Wneg was experienced as more strenuous [90]

Exercise-induced muscle damage and adaptation

A disadvantage of Wneg is temporary and repairable ultrastructural muscle damage, release of muscle proteins in the blood (creatine kinase), loss of function and delayed-onset soreness [93] High mechanical forces generated during Wneg may be responsible for the myofibrillar disorganisation, streaming and disruption of the Z-lines and damage of the connective tissue.[94 95] Muscle soreness and stiffness develop within 48 hours, and is maximal after 24 to 72 hours Complete recovery may take more than a week [96] Adaptation protects the muscle to subsequent damage and occurs rapidly even after a single bout of Wneg.[96] An increase in the mean number of sarcomeres found after decline running in rat vastus intermedius muscle fibres may account for this protection [97]

Eccentric exercise training

Both muscular tension and metabolic cost are stimuli which increase muscle strength [98] In normal subjects, concentric and eccentric exercise training have shown to be equally effective in increasing muscle strength [99] Johnson et al [100] showed that both types of muscle training similarly improved dynamic strength during arm curl and press, and knee flexion and extension Eccentric and concentric exercise increased isometric force of the quadriceps muscle by 11% and 15%, respectively, and cross-sectional area by 5% in both types of exercise.[98] Combined concentric and eccentric resistance training of the quadriceps resulted in a greater increase in concentric peak-torque than concentric training alone.[101] Training with isometric, concentric and eccentric muscle actions increased concentric endurance knee extension exercise also in the elderly [102] The mechanisms of these responses to training are not fully understood. In healthy subjects, heavy resistance leg exercise training increased Type I and Type II fibre area only when both concentric and eccentric muscle actions were performed. Eccentric training did not enhance the capillary proliferation found after concentric training So, muscle fibre hypertrophy was attributed to the greater tension achieved during

eccentric exercise, while capillary density was correlated with the metabolic cost of exercise [103]

If the ventilatory requirements of eccentric exercise are also reduced in patients with COPD, this might be a valuable type of exercise and training especially in patients who have a limited ventilatory reserve and oxygen-uptake capacity The metabolic cost and ventilatory requirements of eccentric exercise and the effects of eccentric exercise training have not yet been investigated in patients with COPD

1.3.4 Conclusions

In patients with moderate to severe COPD, the mechanism of exercise limitation is complex A maximal incremental exercise test is necessary to assess the exercise limitation in individual patients The interpretation of constant work load exercise tests is difficult, as the performance depends on exercise intensity and motivation

Patients with severe COPD may not tolerate exercise intensities, which result in a physiological training response in terms of increased aerobic capacity Therefore, the main goal of training is to improve the performance of daily life activities and to reduce dyspnoea Patients with severe COPD who are hypoxaemic during exercise due to a limitation in oxygen-uptake at the level of the alveolar-capillary membrane, may possibly benefit from supplemental oxygen or eccentric exercise training We hypothesized, that the supplementation of oxygen or eccentric exercise may enable these patients to achieve higher exercise intensities during training, and may thus offer an additional training stimulus Therefore, we undertook a randomized controlled trial of oxygen-supplemented training, and additional eccentric exercise training in comparison with a control training group

1.4 Aims of the study

To investigate the exercise response to single-stage cycle exercise at various constant work loads in patients with severe COPD (Chapter 2)

To investigate the training intensity of a general exercise training regimen in patients with severe COPD (Chapter 3)

To investigate the metabolic cost and ventilatory requirements of eccentric exercise in comparison with concentric exercise in patients with COPD (Chapter 4)

To investigate whether changes in arterial plasma potassium concentrations equally contribute to the exercise ventilation during concentric and eccentric exercise at submaximal work loads (Chapter 5)

To investigate the effects of pulmonary rehabilitation including general exercise training with and without supplemental oxygen on exercise performance and quality of life in patients with COPD and hypoxaemia at peak exercise due to a diffusion-perfusion limitation (Chapter 6)

To investigate whether eccentric exercise training in addition to general exercise training programme additionally improves exercise performance and enhances the physiologic response to training in patients with COPD and hypoxaemia at peak exercise due to a diffusion-perfusion limitation (Chapter 7)

To investigate the long-term effects (1 year) of pulmonary rehabilitation in patients with COPD and hypoxaemia at peak exercise due to a diffusion-perfusion limitation. (Chapter 8)

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CHAPTER 2

Ventilatory steady state during single-stage exercise in patients with chronic obstructive pulmonary disease

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2.1 Abstract

Study objective – During single-stage exercise testing large differences in ventilatory responses have been found between patients with chronic obstructive pulmonary disease (COPD) The aim of the present study was to determine the highest constant work load at which patients with COPD reach a steady state for ventilation (VE), as defined by an increase in VE of less than 10% during at least 3 successive min after the first 4 min of exercise
Patients and methods – Fifteen patients with COPD (mean (SD) FEV_1 1 1 (0 4) L) performed a maximal incremental exercise test (MIT) and single-stage exercise tests (SST) on a cycle ergometer at 60% (SST60%), 45% (SST45%), 30% (SST30%) and 15% (SST15%) of the individual maximum work load (Wmax)
Results – The ventilatory responses showed a wide variety between patients A steady state for VE was achieved in 6 patients during SST60%, in 10 patients during SST45% and in 11 patients during SST30% During SST15% 3 patients did not reach a steady state The ventilatory threshold (VT) work level, as determined by the V-slope method during MIT, corresponded with the highest achievable steady-state work rate and oxygen consumption (VO_2) in only 4 and 6 patients, respectively All 6 patients in whom Wmax and VO_2 exceeded 75 W and 1 L/min, respectively, reached a steady state at SST45% If exercise capacity was below these values, the work rate at which a steady state was achieved varied
Conclusions – Most patients with COPD reach a steady state for ventilation during exercise at a constant work load of less than 60% of maximum

2.2 Introduction

Endurance in normal subjects is assessed during submaximal exercise tests by measuring how long a constant work load can be sustained.[1,2] In patients with chronic obstructive pulmonary disease (COPD), many protocols for single-stage cycling and treadmill walking have been described. In these studies, the work load varied between 40 and 80% of the individual maximum work load and was chosen on the basis of parameters derived from a maximal incremental exercise test, such as the maximal work capacity[3-7] or the anaerobic threshold.[8-10] In these patients, single-stage tests may reflect the ability to perform daily life activities. Endurance time appeared to be more sensitive to improvement after training than maximal exercise capacity.[4,6,9-12] However, the variability in exercise responses between patients was large. Lactate production during single-stage exercise at high and low work rates varied. A steady state was achieved in some patients, while in others no differences in exercise response were found between single-stage and maximal incremental exercise.[4,9,10,12] The pathophysiologic bases of the cardio-respiratory impairment and the physical fitness of the patient may account for these differences in exercise response.

A true steady state is achieved when the oxygen consumption and carbon dioxide production remain constant, while exercise is being continued.[13] In patients with COPD, this will be achieved only when the ventilatory requirements during exercise do not exceed the ventilatory capacity. The purpose of the present study was to determine the highest constant work rate at which a steady state for ventilation was reached in patients with COPD. In addition, we investigated whether it was possible to predict this constant work rate from age, body mass, lung function parameters, or from data obtained during MIT.

2.3 Methods

Study population

Fifteen patients (10 male) with COPD according to ATS criteria[14], who were referred to our centre for pulmonary rehabilitation, participated in the study. All patients used inhaled β_2-adrenergics and corticosteroids, 13 of them used oral theophylline. None of them were treated with oral corticosteroids. They had been in a stable clinical condition for at least 4 weeks and were familiar with the procedures of exercise testing. All patients were non- or exsmokers. They had no cardiovascular disease and a normal ECG. Informed consent was obtained from each patient. The study was approved by the hospital ethical committee.

A complete pulmonary function study was performed according to ERS-standards.[15] Maximal sniff inspiratory oesophageal pressure ($P_{I_{oes,max}}$) was measured with a balloon catheter, which was connected to a pressure transducer (Validyne

DP103-32, Northridge, California) Maximal sniff manoeuvres from residual volume were performed in sitting position until the highest pressure was achieved [16]

Exercise protocol and measurements

Exercise tests were performed on an electrically-braked cycle ergometer (Lode, Groningen, The Netherlands) The patients cycled at a pedalling rate of 60 revolutions per minute (RPM), breathing ambient air During a symptom-limited maximal incremental exercise test (MIT) the work rate increased each minute by 10% of the predicted maximal work load (Wmax) [17] Arterial blood samples were taken from an indwelling catheter in the brachial artery at rest, at maximum and after 3 min of recovery and analysed immediately (Ciba Corning 178 DMS, Houten, The Netherlands) Heart rate (HR) was monitored by one lead ECG recording (V5) Minute ventilation (VE), oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured every 30 seconds by a mixing chamber ergospirometry unit (Oxycon IV, Mijnhardt, Maarsen, The Netherlands) At the end of the test the cycling time was recorded and dyspnea was scored on a modified Borg scale [18] HR and VE were related to predicted maximal values (predicted HRmax = 220-age[1], predicted VEmax = 37,5 x FEV_1) [19] The ventilatory threshold (VT) was estimated by the V-slope method [20]

Single-stage exercise tests (SST) were performed on separate occasions with a maximum of two tests on the same day and a period of rest of at least 4 h During the first minute the patients cycled without any external load Subsequently, they exercised at a work rate of 60%, 45%, 30% or 15% (SST60%, SST45%, SST 30%, SST15%) of the individual Wmax The tests were terminated when the patient could not sustain exercise any longer, or after a maximum of 15 min The same measurements were performed as during MIT, except for blood gas analysis Arterial oxygen saturation (SaO_2) was monitored with a pulse oximeter (Oxy-shuttle, Sensor Medics, Bilthoven, The Netherlands) A steady state for ventilation was accepted when VE increased by less than 10% during at least 3 consecutive minutes after the first 4 minutes of exercise [28]

Statistical analysis

Results were expressed as mean values (SD) Differences between maximal incremental exercise and single-stage exercise were compared with the Wilcoxon test for paired samples and corrected for multiple measurements Steady-state work load and oxygen consumption were correlated with independent variables with the Spearman correlation coefficient Significance was accepted at a p-value less than 0 01

2.4 Results

The characteristics of the patients are summarized in Table 2.1. The transfer coefficient for carbon monoxide (KCO) was below the normal range (mean (SD) 46 (25)% of predicted) and one patient was hypoxic at rest (PaO_2 7 1 kPa). $P_{I_{oes\ max}}$ was 6 8 (3 3) kPa (range 3 4 to 13 7 kPa) and was in the same range as has been reported before in patients with respiratory muscle weakness [21]

Table 2 1 Patient characteristics

Patients, *n*	15
Age, *yrs*	61±9
Weight, *kg*	69±8
Height, *cm*	173±9
BMI, kg/m^2	23±4
TLC, *L*	6 8±2 3
TLC % predicted, %	110±22
IVC, *L*	3 6±1 3
IVC % predicted, %	96±20
FEV_1, *L*	1 1±0 4
FEV_1 % predicted, %	36±11
KCO % predicted, %	46±25
PaO_2 rest, *kPa*	10 2±1 8
$PaCO_2$ rest, *kPa* (n=14)	5 1±1 0
$P_{I_{oes\ max}}$, *kPa*	6 8±3 3

Values are presented as mean±SD BMI body mass index, TLC total lung capacity (He-dilution), IVC inspiratory vital capacity, FEV_1 forced expiratory volume in one second, KCO transfer coefficient for carbon monoxide (single-breath), PaO_2 arterial oxygen tension, $PaCO_2$ arterial carbon dioxide tension, $P_{I_{oes\ max}}$ maximal inspiratory oesophageal pressure

Maximal incremental exercise test (MIT)

All patients stopped because of dyspnoea. Wmax was 76 (41) W (range 30 to 160 W). Peak VO_2 was 1 14 (0.43) L/min (range 0.61 to 2.07 L/min) (Table 2.2). During exercise PaO_2 fell from 10.2 (1.8) to 7 3 (0.9) kPa. $PaCO_2$ rose from 5.1 (1 0) to 5.9 (1.1) kPa, and peak VE was 90% (28%) of predicted, indicating a ventilatory limitation (Table 2.2). The change in base excess during the test (Δbase excess) was -5.8 (2 5) mmol/L (range 1 7 to 9 6 mmol/L). pHa decreased from 7.432 (0 04) to 7.342 (0.06)

Table 2.2 Exercise responses to a maximal incremental exercise test (MIT) and to single-stage exercise tests (SST) at various constant work loads

	MIT	SST60%	SST45%	SST30%	SST15%
HR, *beats/min*	134±19	127±19*	121±15*	113±12*	104±13**
HR %HRmax pred., %	85±12	80±11*	76 ±9*	72±8*	66±9**
VE, *L/min*	36±15	33±14*	29±10*	26±7*	22±5**
VE %VEmax pred., %	90±28	84±26*	74±17*	67±16*	59±16**
VO_2, *L/min*	1.14±0 43	1.06±0.38	0.91±0.24*	0.82±0.16*	0.68±0.12**
VCO_2, *L/min*	1.15±0.47	1.02±0.42	0.85±0.24*	0.73±0.15**	0.63±0.13**
VE/VO_2	31.8±5.8	31.8±6.7	32.0±5 7	31 7±6.0	33.1±5.2
SaO_2, %	86±4	85±5	88±5*	89±6*	91±5*
Cycling time, *min*	6.1±2.3	7.5 ±5.3	10.3±5.6*	11.8±5.6**	11.9±5.4**
Dyspnoea, *Borg scale*	6.6±1.7	6.1±1.4	5.6±1 6	3.5±1.8*	3 4±2.0*

Values are presented as mean±SD. MIT: maximal incremental exercise test; SST60%, SST45%, SST30%, SST15%: single-stage exercise test at a constant work load expressed as percentage of maximum; HR: heart rate; VE: minute ventilation; VO_2: oxygen consumption, VCO_2: carbon dioxide production; VE/VO_2: ventilatory equivalent for oxygen; SaO_2: arterial oxygen saturation.

* $p<0.01$; ** $p<0.001$: comparison between SST and MIT.

Single-stage exercise tests (SST)

Large differences were found in the exercise responses between patients. HR, $\dot{V}E$, $\dot{V}O_2$, SaO_2 and Borg score decreased and cycling time increased as the constant work load decreased (Table 2.2). The individual time courses of VE during the single-stage exercise tests are shown in Figure 2.1. Six patients (Pat. 1, 5, 7, 9, 12, 13) reached a ventilatory steady state during SST60%, 10 patients (Pat. 2, 3, 6, 14) during SST45% and 11 patients (Pat. 11) during SST30%. During SST15% 3 patients (Pat. 4, 10, 15) were still not able to reach a steady state. When a steady state was not achieved during SST, the time course of $\dot{V}E$ was identical with that during MIT. In 9 patients, the cycling time during SST60% was the same as during MIT or less.

The VT could not be detected by the V-slope method in 4 patients during MIT, although in 3 of them base-excess had decreased by more than 5 mmol/L. The VT work rate and $\dot{V}O_2$ corresponded with the highest achievable steady-state work rate and $\dot{V}O_2$ during SST in 4 and 6 patients, respectively.

Prediction of the highest achievable steady-state work level

To predict the highest work load and oxygen consumption at which a steady state may be reached (n=12), these values were correlated with multiple physiologic parameters as independent variables (Table 2.3). The highest achievable steady-state

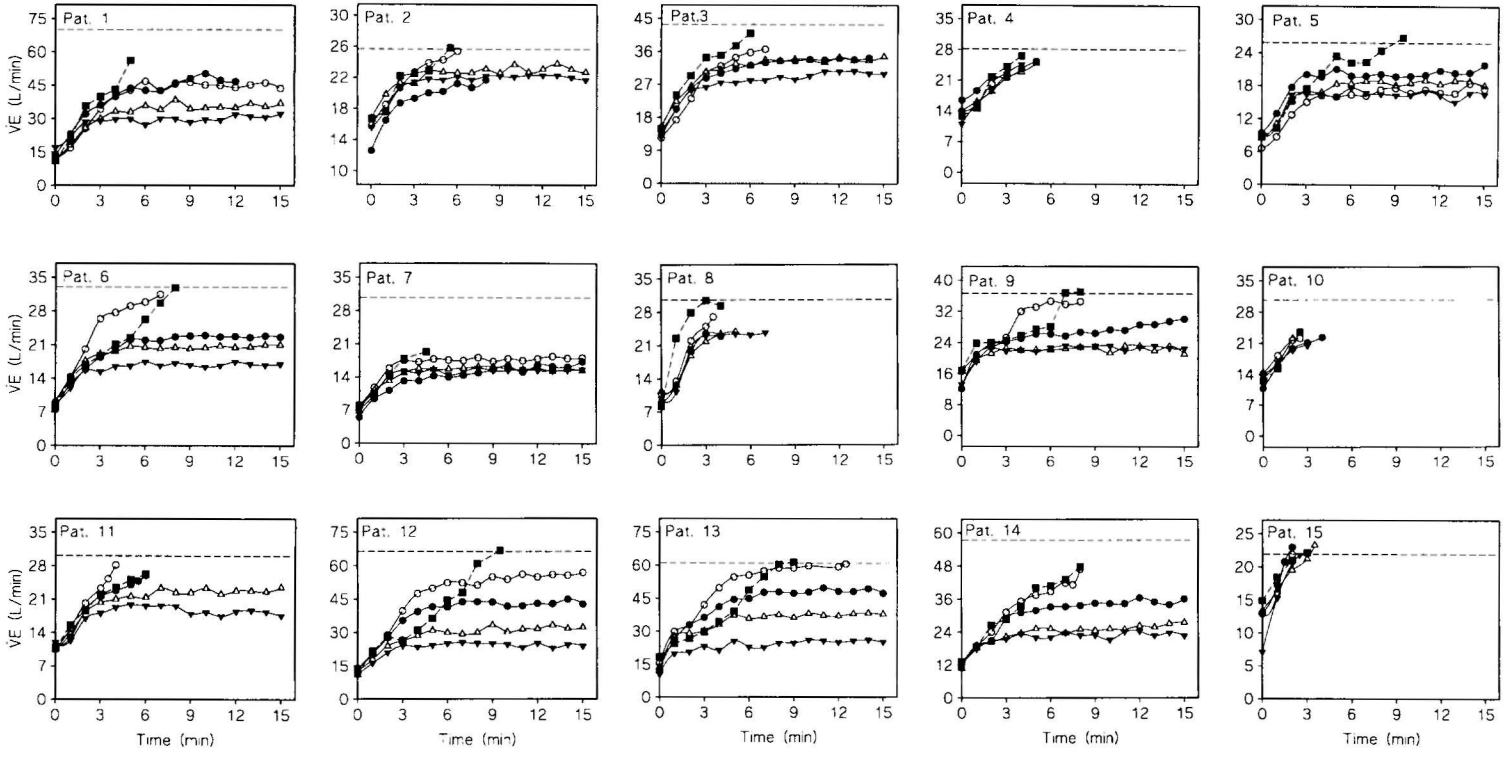

Figure 2.1 The individual time courses of minute ventilation (V̇E, L/min) in 15 patients with COPD during a maximal incremental exercise test (MIT; closed squares, broken line) and during 4 single-stage exercise tests (SST) at different work loads: 60% (SST60%; open circles), 45% (SST45%; closed circles), 30% (SST30%; open triangles) and 15% (SST15%; closed triangles) of the maximum work load. The straight horizontal broken line represents predicted maximal exercise V̇E for each patient.

Table 2 3 Spearman correlations of independent variables with the highest achievable steady-state work load (r_1) and oxygen consumption (r_2)

	r_1	r_2
Age	-0.04	-0.30
Weight	0 07	0.30
BMI	0.25	-0.31
Lung function		
TLC	0 13	0.17
TLC %predicted	0 25	0 28
IVC	0.32	0.59
IVC %predicted	0 56	0.43
FEV_1	0 52	-0 19
FEV_1 %predicted	0 41	-0.24
KCO %predicted	0 29	0.13
$P_{I_{oes\ max}}$	0.45	0.33
Maximal Incremental Exercise Test		
Wmax	0.61	0.86*
Peak HR	0.62	0 44
HR %HRmax pred.	0 64	0.28
Peak VE	0.54	0.88*
VE %VEmax pred.	0.54	0.34
Peak VO_2	0 67*	0.93*
Peak VCO_2	0 57	0.93*
$VE/\dot{V}O_2$	-0.04	0.39
VE/VCO_2	0 03	0 27
PaO_2	0 36	0 36
ΔPaO_2	-0.46	-0.59
$PaCO_2$	-0.18	-0.48
$\Delta PaCO_2$	0 14	-0.22
ΔBase excess	0.23	0.49
ΔpHa	0.46	0.50
VD/VT	-0.46	-0.35
ΔVD/VT	-0.11	0.02
Dyspnoea	0.32	0.08

VE/VCO_2: ventilatory equivalent for carbon dioxide; VD/VT: dead space/tidal volume ratio; Δ indicates the change during exercise testing. For further definitions see legends to Tables 2.1 and 2.2.

* $p<0.01$: Spearman correlation coefficient.

$\dot{V}O_2$ showed a good correlation with Wmax (r=0.86, p<0.005), and peak $\dot{V}O_2$, $\dot{V}CO_2$ (both values r=0.93, p=0.002) and $\dot{V}E$ (r=0.88, p=0.004). All patients in whom Wmax and peak $\dot{V}O_2$ exceeded 75 W and 1 L/min, respectively, achieved a steady state at SST 45%. When maximal exercise capacity was below these values, the response to SST varied widely (Figure 2.2). Age, body mass index (BMI), lung function, $P_{I_{oes,max}}$ and Δbase excess during MIT did not correlate with highest achievable steady-state work rates (Table 2.3).

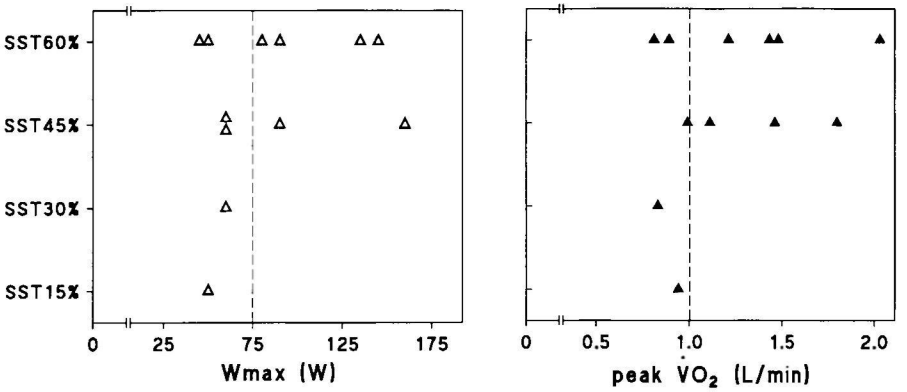

Figure 2.2. The single-stage exercise test at the highest constant work load during which a steady state for ventilation was achieved is plotted against the maximum work load (Wmax, open triangles; left panel) and peak oxygen consumption (peak $\dot{V}O_2$, closed triangles; right panel) for each patient (n=15). For further definitions see legends to Figure 2.1. Three patients did not achieve a steady state during any of the single-stage tests. Six patients, in whom Wmax exceeded 75 watts and peak $\dot{V}O_2$ was more than 1 L/min, reached a steady state during SST45%.

2.5 Discussion

In this study, large differences were found in the highest sustainable steady-state work load between patients with COPD, especially when Wmax was less than 75 W and peak $\dot{V}O_2$ was less than 1 L/min. Even at a work rate as low as 15% of Wmax, 3 out of 15 patients did not reach a ventilatory steady state.

Similar responses to single-stage cycle exercise have been reported by Matthews et al.[6] and Casaburi et al.[9] During exercise at a constant work rate of approximately 75% of Wmax, HR, $\dot{V}E$, $\dot{V}O_2$ and lactate were not different from values achieved during maximal incremental exercise. In the study of Casaburi et al.[9], 8/19 patients could not accomplish an exercise test of 15 min at a constant work load of approximately 40% of Wmax. In both studies, FEV_1 (55% of predicted) and peak $\dot{V}O_2$ (1.5 L/min) were higher than in our patients, and hypoxia did not

occur at Wmax.[6,9] Other investigators found similar cycling times during incremental exercise and single-stage exercise at approximately 65% and 40% of Wmax.[11,12]

In healthy subjects, the highest work rate that can be sustained mainly depends on physical fitness, work efficiency, energy stores and motivation [1,22] A steady state for VE, VO_2 and VCO_2 may be reached within 4 min of exercise below the anaerobic threshold work rate At work rates above the anaerobic threshold, the accumulation of lactic acid will cause VCO_2 to increase more rapidly than VO_2. As a result, a ventilatory steady state is achieved at a later point of time during exercise, or is not achieved at all In patients with COPD, accumulation of lactate has been observed during exercise at work rates below 50% of Wmax and even during unloaded pedalling, which was possibly due to poor physical fitness [9] It is obvious that these patients will have difficulty in reaching a ventilatory steady state even at very low work loads.

Although the VT is an important determinant of steady state, many other factors may affect the ventilatory response during exercise in patients with COPD. Impairment of pulmonary mechanics, dynamic hyperinflation, increased dead space ventilation, ventilation to perfusion inhomogeneity, reduced diffusion capacity and respiratory muscle function as well as reduced cardial function may all limit exercise performance before lactate accumulates.[2,9,20,23,24] In a study of Nery et al [8], 8 out of 9 patients (mean FEV_1 1 1 L) did not reach the anaerobic threshold during exercise at a constant work rate of 50% of Wmax However, the time needed to reach a steady state for VE was increased in patients with COPD in comparison with normal subjects, which was attributed to a slower cardiovascular response.[8]

In our study, the change in base excess during MIT showed no correlation with the highest achievable steady-state work level Furthermore, gas exchange parameters for the determination of the VT were not reliable, which is in agreement with previous reports [23] In 3 patients, we failed to detect the VT by the V-slope method during MIT. In 7 patients, the estimated VT work level differed (in 5/7 patients the VT work rate was lower) from the work rate at which steady state was achieved during the single-stage tests In the patients who had exercised above VT during MIT, we expected VE/VO_2 to be lower during single-stage exercise, when work was performed below VT. However, VE/VO_2 did not differ between MIT and any of the single-stage tests, as was also reported by Casaburi[9]. This was found in spite of a higher SaO_2 during SST, which also might have reduced VE/VO_2.[5,9,25] Probably, the mechanisms involved in the ventilatory steady state in patients with COPD are complex and may vary individually

In the present study, the value of Wmax and peak VO_2 as predictors of the highest achievable steady-state work rate or VO_2 was limited to patients with higher exercise capacities. In these subjects, whose physical fitness is better, the relative contribution of the respiratory muscles to the total amount of work may be less [26,27] Although respiratory muscle weakness was related to maximal work

capacity in patients with COPD [28,29], we did not find any correlation between $PI_{oes\ max}$ and highest achievable steady-state work rates Conflicting data exist about the value of lung function parameters, anthropometric data and ratings of perceived exertion as predictors of maximal work capacity [30,34] In our study, they were not correlated with highest achievable steady-state work rates either

We conclude, that in patients with COPD the description of single-stage tests as "submaximal tests", "steady-state tests" or "endurance tests" may be inappropriate for work loads exceeding 45% of Wmax If Wmax is less than 75 W and peak VO_2 is less than 1 L/min, the constant work load that results in a steady state may be very low, and has to be determined individually

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CHAPTER 3

Cardio-respiratory load of exercise training in patients with severe COPD

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Submitted

3.1 Abstract

Study objective – The effect of physical training depends on the intensity at which exercise is performed Patients with chronic obstructive pulmonary disease (COPD) may not tolerate high exercise intensities during training due to breathlessness The purpose of the present study was to investigate the cardio-respiratory load of exercise training, during pulmonary rehabilitation, in patients with severe COPD We also studied the effects of pulmonary rehabilitation on maximum exercise performance

Patients and methods – Thirteen patients with stable COPD (FFV_1 (SD) 1 0 (0 3) L) performed an incremental cycle exercise test at baseline and after a 10-wk in-patient pulmonary rehabilitation programme Exercise training consisted of dynamic and isometric strength training exercises, and training of specific daily life activities

Training sessions were held 5 days per week for 10 weeks Heart rate (HR) and dyspnoea ratings (Borg scale) were measured during one session in the second or third week of training, and were compared with values obtained during incremental cycle exercise at baseline The ventilatory load during the training was estimated by using the relationship between HR and minute ventilation (VE) during incremental cycle exercise at baseline

Results – The duration of a training session was 80 (7) min, including periods of rest The HR during various exercises of the training programme varied between 94 (17) and 103 (14) % of peak HR during incremental cycle exercise Borg scores during the training varied between 2 0 and 5 7, and were lower than the Borg score at peak exercise (6 5 (2 0)) HR was more than 90% of peak HR during 36 (33) min of the whole training session, which corresponded with a VE of 81 (11) % of peak VE during incremental cycle exercise Training significantly increased Wmax from 62 (25) to 73 (21) W ($p<0\ 05$), without any change in peak HR, VE and VO_2

Conclusions – In patients with severe COPD, the training intensity in terms of cardio-respiratory load was high in relation to individual maximum values Pulmonary rehabilitation, including exercise training, improved maximum exercise performance

3.2 Introduction

Patients with chronic obstructive pulmonary disease (COPD) experience disabilities and handicaps as a result of their ventilatory impairment Pulmonary rehabilitation has been defined as an ongoing multidimensional process with the aim of improving functional capacity and quality of life in these patients [1] The goals of pulmonary rehabilitation are achieved by an accurate diagnosis and evaluation of exercise limitation, optimalizing medical treatment, exercise training, physical therapy, breathing retraining, nutritional advice, education and psycho-social support [1 3] The benefits of pulmonary rehabilitation in patients with COPD have been well established [4]

Exercise training is an important component of pulmonary rehabilitation and should take place 3-5 days/week [1 2] Many training regimens varying in exercise modalities, frequency and duration have shown beneficial effects on exercise tolerance [5] Endurance exercise training may result in a physiologic training effect, also in patients with severe COPD [6 8] However, many of these patients do not tolerate high exercise intensities due to pulmonary impairment and breathlessness In a recent study, Maltais et al reported exercise intensities increasing from 25 to 65% of the individual maximum exercise capacity during a 12-wk endurance training programme [8] The exercise intensity in terms of cardio-respiratory load has not been well documented [6 8]

This paper describes a comprehensive in-patient pulmonary rehabilitation programme for patients with severe COPD To investigate the exercise intensity of our exercise training programme, heart rate and dyspnoea ratings (Borg scale) were measured during a training session and related to values achieved during incremental cycle exercise Furthermore, we evaluated the effects of pulmonary rehabilitation on maximum exercise performance

3.3 Methods

Study population

Thirteen patients with stable COPD[2] entered the study All were referred for pulmonary rehabilitation All patients were normoxic at rest and had no neuromuscular or cardiovascular disease They were all ex-smokers Their medication was not changed during the study They were familiarized with the procedures of exercise testing before the start of the study Informed consent was obtained from each patient The study was approved by the hospital ethics committee

Pulmonary rehabilitation programme

Pulmonary rehabilitation as carried out in our clinic comprises initial assessment, intervention and follow-up The interdisciplinary team comprises a physician, a

pulmonary physiologist, nurse, physical therapist, exercise therapist, dietician, social worker, psychologist and art therapist. Intervention consists of a comprehensive in-patient programme for 10 weeks, 5 days/week, and includes exercise training, breathing retraining, physical therapy, education and psycho-social support The partner and close relatives are involved in the treatment as much as possible.

During their stay the patients learn to manage daily household tasks such as making their own bed, preparing meals, and washing the dishes. Plans are worked-out to continue exercises at home and to participate in maintenance exercise groups and in recreational activities after discharge. Patients who need home care are referred to primary health care services. Evaluation takes place during an out-patient visit approximately 2 months after completion of the programme.

Exercise training programme

The aim of physical training is to improve muscle strength and endurance, mechanical skill, coordination and efficiency and to reduce breathlessness. For this purpose, a general exercise training programme has been developed consisting of dynamic and isometric strength training exercises, and training of specific daily life activities.[5] All patients performed whole body exercise, and exercise by different muscle groups of upper and lower extremities.(Table 3.1) Because of the reduced ventilatory reserve, interval training and bouts of exercise of short duration were used. Training sessions were held 5 days per week and were supervised by a physical (exercise) therapist. Attention was paid to the control of breathing, and to pursed-lip breathing during exercise[9] SaO_2 was monitored with a pulse oximeter using a finger-probe (Oxyshuttle, Sensor Medics, Bilthoven, The Netherlands). Supplemental oxygen was supplied if necessary to keep SaO_2 above 90% Training exercises were started at low work loads, which were gradually increased during the first week. Afterwards, exercise training was performed at the highest intensity that could be tolerated.

Apart from the daily training sessions, the patients joined activities, which were held once or twice weekly and included indoor games, swimming, sauna and outdoor activitiesm, such as walking and cycling.

Measurements

Spirometry and transfer coefficient for carbon monoxide (single-breath) were performed according to European Respiratory Society (ERS) standards.[10]

A maximal incremental exercise test on an electrically-braked cycle ergometer (Lode, Groningen, The Netherlands) was performed before and after pulmonary rehabilitation. The patients cycled at a pedalling rate of 60 revolutions per minute (RPM), while breathing room air. The work rate was increased each minute by 10% of the estimated maximum work load (Wmax), until exhaustion [11] Arterial blood samples were drawn from an indwelling catheter in the brachial artery Minute ventilation (VE) and oxygen consumption (VO_2) were measured every 30 s

Table 3.1 Exercise training programme

Training exercise	Duration (min)	HR (SD) (beats/min)	BORG score (SD)
Interval cycling Five periods of 2 min of exercise on a cycle ergometer and 2 min of rest.	20	121 (15)	4.9 (1 4)
Rowing continuing exercise on a rowing machine.	5	129 (15)	5 0 (1 8)
Dynamic exercise of arm and shouldergirdle using a pulley	5	117 (16)	3.5 (1.7)
Dynamic exercises for the muscles of the back and abdomen Lifting the upper body and the legs, respectively, from supine position with the knees bent.	5	117 (16)	3 5 (1.5)
Isometric strength training of the arms, shouldergirdles and legs Five repititions of maximal contraction which can be maintained for 6 sec. Both upper extremities are trained simultaneously by using weights, which the patient has to lift up from the floor while sitting upright. The right and left leg are trained separately on an exercise equipment.	3	-	-
Stair-climbing Exercise is performed on a staircase with a hand-rail, which has 4 steps for going up, a plateau and 3 steps for going down	3	124 (18)	5 7 (2 2)
Sitting down and getting up from a chair alternated with 3 m of slalom walking	5	120 (16)	4.4 (2 0)
Weight-lifting exercise A dumbbell of 1-2 kg is placed into a rack alternatingly at 20 cm above and below shoulder level. The left and right arm are trained separately for 2,5 min.	5	116 (17)	2 0 (1 6)

by a mixing chamber ergospirometry unit (Oxycon IV, Mijnhardt, Maarsen, The Netherlands). Heart rate (HR) was recorded by one lead electrocardiogram (ECG) Dyspnoea at peak exercise was scored on a modified Borg scale (range 0-10) [12]

During one training session in the second or third week of pulmonary rehabilitation, HR was continuously monitored with a device (PE Sport Tester 3000S, Polar Electro, Finland), which records the mean HR during consecutive periods of 5 s. The start and end of each exercise could be marked on the recording by an electric signal The data were stored, and analysed by computer afterwards HR during isometric strength training was not analysed separately because of the short duration of this type of exercise Except for the latter, dyspnoea was scored at the end of each training exercise. HR and Borg scores during the training were compared with those achieved during the incremental cycle exercise test at the start of the study. The individual relationship between HR and minute ventilation (VE) during incremental cycle exercise was used to estimate VE during the training in each patient. For evaluation of the whole group, HR was expressed as percentage of peak HR achieved during incremental cycle exercise, and as percentage of predicted maximal (age specific) HR (predicted HRmax = 220-age)[13], VE was expressed as percentage of predicted maximal exercise ventilation (predicted VEmax = 37,5 x FEV_1.[14]

Statistical analysis

The results were expressed as mean and standard deviation (SD) Changes within the training groups were compared with the Wilcoxon test for paired samples The correlation between various parameters was tested with the Spearman correlation coefficient. Significance was accepted at a p-value of less than 0 05.

3.4 Results

The patients had severe airway obstruction and emphysema as suggested by hyperinflation. They had a reduced transfer coefficient for carbon monoxide, but they were normoxic at rest (Table 3 2)

During incremental cycle exercise, the peak HR was 125 (18) beats/min, which was 78 (13) % of predicted HRmax (range 57-94%). VE was 99 (20) % of predicted VEmax (range 70-129%) PaO_2 decreased by almost 2 kpa, $PaCO_2$ increased by 0.4 kPa Base excess decreased due to lactic acidosis by 5.7 mmol/L (range 0 9 to -10.2 mmol/L) (Table 3 3).

The slope of the relationship between HR and VO_2, and between HR and VE during incremental cycle exercise showed a wide range between subjects (Figure 3 1)

The mean duration of one training session was 80 (7) min including periods of rest. The mean HR during different training exercises varied between 116 (17)

Table 3.2 Patients characteristics

Patients, *n*	13
Sex, *M/F*	10/3
Age, *yrs*	59±11
TLC %predicted, *%*	119±22
FRC %predicted, *%*	153±29
RV %predicted, *%*	154±34
IVC %predicted, *%*	101±20
FEV_1, *L*	1.0±0 3
FEV_1 %predicted, *%*	31±8
KCO %predicted, *%*	33±14
Heart rate, *beats/min*	93±13
PaO_2, *kPa*	10.1±1.2
$PaCO_2$, *kPa*	5 0±0.4

Values are presented as mean ± SD Reference values were derived from Quanjer.[10] TLC: total lung capacity (He-dilution); FRC. functional residual capacity, RV residual volume; IVC. inspiratory vital capacity, FEV_1· forced expiratory volume in one second; KCO transfer coefficient for carbon monoxide (single-breath); HR: heart rate; PaO_2 arterial oxygen tension; $PaCO_2$ arterial carbon dioxide tension

Table 3 3 Maximal incremental cycle exercise before and after pulmonary rehabilitation

	before	after
Wmax, *W*	62±25	73±21*
HR, *beats/min*	125±18	125±18
HR %HRmax pred , *%*	78±13	78±12
VE, *L/min*	38±8	39±9
VE %VEmax pred., *%*	99±20	101±24
VO_2, *L/min*	1.10±0 19	1.13±0.19
VE/VO_2	34 9±5 8	35.1±5.2
O_2 pulse, *mL/beat*	9 1±2.0	9 6±2 6
Wmax/peak HR, *W/(beats/min)*	0 50±0.20	0 59±0.17
Wmax/peak VO_2, *W/(L/min)*	55 3±17.9	63 4±10.5
PaO_2, *kPa*	8.1±1.2	7.9±1.2
$PaCO_2$, *kPa*	5.6±0.9	5.5±0.7
ΔBase excess, *mmol/L*	-5.1±2.7	-6.4±3 0
Dyspnoea, *Borg scale*	6.5±2.0	6 5±2.1

Values are presented as mean ± SD. Wmax maximum work load, VE. minute ventilation; VO_2· oxygen consumption; VE/VO_2 ventilatory equivalent for oxygen, Δbase excess. change in base excess. For further definitions see legend to Table 3 2.
*p<0 05 within-group comparison before versus after pulmonary rehabilitation

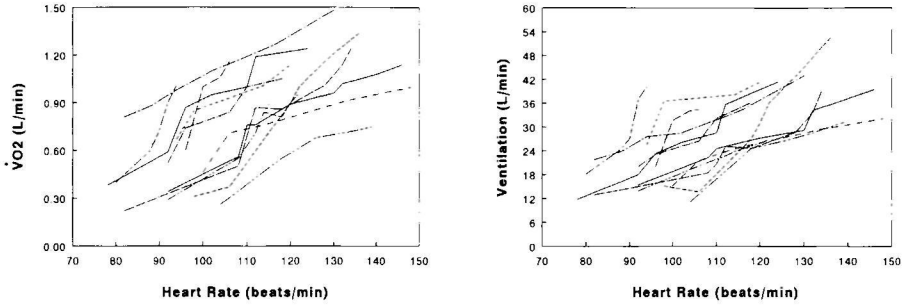

Figure 3.1 The relationship between heart rate (HR) and oxygen consumption ($\dot{V}O_2$) (left panel), and between HR and minute ventilation ($\dot{V}E$) (right panel) during maximal incremental cycle exercise. Each line represents one patient (n=13).

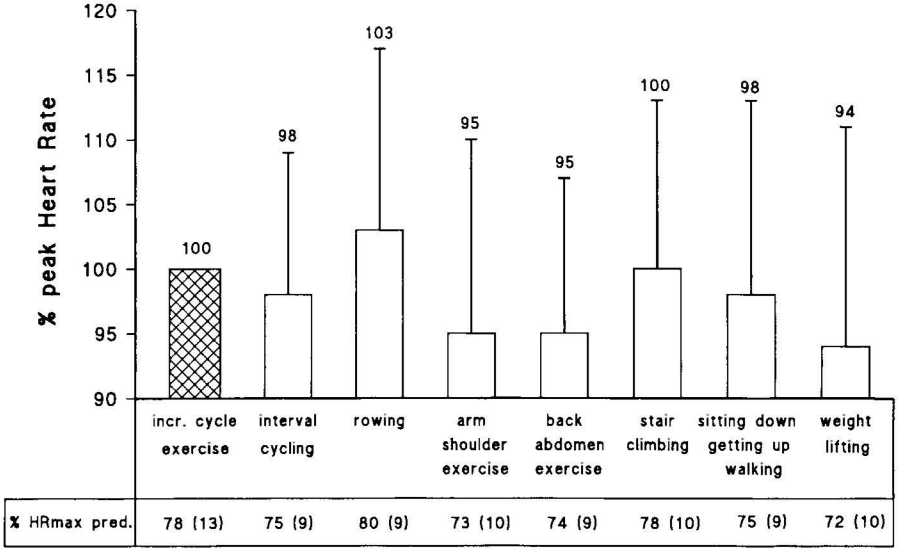

Figure 3.2 Mean heart rate (HR), expressed as percentage of peak heart rate during maximal incremental cycle exercise (peak HR; crossed bar), achieved during different training exercises (open bars): interval cycling; rowing; dynamic arm and shouldergirdle exercise using a pulley; dynamic exercises for the muscles of the back and abdomen; stair-climbing; sitting down, getting up from a chair and slalom walking; weight-lifting. Error bars represent standard deviation. HR is also expressed as percentage of predicted maximal heart rate (HRmax pred.).

beats/min during weight-lifting and 129 (15) beats/min during rowing (Table 3.1). Consequently, HR varied between 94 (17) and 103 (14) % of peak HR, and between 72 (10) and 80 (9) % of predicted HRmax (Figure 3.2).

The HR during the whole training session was 57 (25) min above 80% and 36 (33) min above 90% of peak HR during incremental cycle exercise. These

heart rates corresponded with a VE of 64 (17) and 81 (11) % of peak VE, respectively.

The ratings for perceived exertion during the training exercises were less than during incremental cycle exercise. The Borg scores varied between 2.0 (1 6) during weight-lifting and 5.7 (2 2) during stair-climbing (Table 3 1) A significant correlation was found between Borg score and HR (r=0.94, p=0 03)

After pulmonary rehabilitation, Wmax significantly increased by 11 (19) W (p=0.05) This was achieved at a similar HR, VE, VO_2, PaO_2, $PaCO_2$ and Borg score at peak exercise. The further decrease in base excess by 1 3 mmol/L was not significant (Table 3.3).

3.5 Discussion

In the present study, the training intensity in terms of cardio-respiratory load was investigated in patients with severe COPD. Training was performed at the highest exercise level, which could be tolerated by the patients. During all training exercises, the mean HR exceeded 70% of predicted HRmax, and 90% of the individual peak HR during incremental cycle exercise. Thus, training intensity was high, which may have contributed to the improvement in maximum exercise performance.

In normal subjects, a training stimulus is obtained at exercise intensities above the anaerobic threshold, *ie* levels exceeding 70% of VO_2max or 75% of predicted HRmax, as HR is closely correlated with VO_2 [13] Training sessions should be at least 20 min in duration, and should be held 3-5 days/week for 5-10 weeks.[5]

In contrast to normal subjects, patients with COPD are ventilatory limited during exercise. Impaired pulmonary mechanics, gas exchange disturbances and increased lactate levels change the HR to VO_2 relationship during exercise. For a given VO_2, HR (and VE) are higher in patients with COPD than in normal subjects. During progressive exercise, these patients cannot meet the ventilatory requirements of exercise and stop because of dyspnoea. As a result, maximal exercise capacity is reduced, and predicted HRmax may not be reached.[15] Thus, HR is not a reliable indicator of a physiologic training effect in patients with COPD. The present study further showed, that the slope of the relationship between HR and VO_2 during incremental cycle exercise varied widely between subjects. This means that the use of HR to estimate training intensity should be individualized.

Therefore, HR during the training was correlated with HR during the incremental cycle exercise test in each individual patient To estimate the ventilatory load during the training, HR during the training was correlated with VE at corresponding HR's during incremental cycle exercise. During at least 20 min of the training session, HR was above 80% of peak HR in 12/13 and more

than 90% in 6/13 patients. This corresponded with a $\dot{V}E$ of more than 60% of peak VE in 9/13 patients. Thus, exercise training was performed at a high HR and exercise ventilation, relative to individual maximum exercise values. In patients with severe COPD, Casaburi et al.[7] found that the HR during endurance cycle exercise training at work rates up to 100% of Wmax was approximately 90% of peak HR during incremental cycle exercise. In the present study, the relationship between HR and $\dot{V}E$ during incremental exercise, as well as peak exercise values of HR, VE and Borg score remained unchanged after training. Thus, HR may be used as an indirect parameter of exercise intensity throughout the training period. This, however, does not imply that a physiologic training effect is obtained. Only 7/13 patients, in whom base excess during incremental cycle exercise decreased by more than 4 mmol/L, might have reached the lactate threshold during training.[13]

The patients in the present study exercised at the highests tolerable work level. However, the Borg scores during various training exercises did not reach values achieved at peak exercise during incremental cycle exercise. This is explained by the training regimen comprising exercises for different muscle groups, which were performed with intervals or in short bouts. Since Borg score correlated with HR during training, dyspnoea scores may be used as a training intensity target. This is in agreement with a recent study showing that dyspnoea ratings, using the relationship between dyspnoea ratings and VO_2 during an incremental cycle exercise test, may estimate the training intensity for the same type of exercise in individual patients.[16] The results of the present study suggest, that dyspnoea scores can be used for other training exercises also. It is not evident, however, that the target dyspnoea score is the same for various training exercises.

Many studies have reported beneficial effects of pulmonary rehabilitation in patients with moderate to severe COPD.[6 8,17 24] A physiologic training effect of exercise training may be difficult to achieve in patients with COPD, as it depends on the severity of the disease, the physical fitness, the training intensity and the ability to exercise above the anaerobic threshold. In patients with moderate airway obstruction (FEV_1 56% of predicted), Casaburi et al. found reductions in HR, ventilation and blood lactate concentrations at similar work rates after training. Training at a high work rate above the anaerobic threshold or at 80% of VO_2max was more effective than training at a low work rate.[6]

In patients with severe COPD, an improvement in aerobic capacity after training has been reported in some studies[7 8 20 22 24], whereas others did not find an increase in peak VO_2, or a decrease in HR relatively to VO_2 after training.[17 19] Recently, Maltais et al. reported a reduction in $\dot{V}E$ and blood lactate concentration at iso work rates in patients with severe COPD (FEV_1 38% of predicted) after training. In their study, endurance training (30 min, three times a week) was performed on a cycle ergometer at moderate training intensities up to 65% of the individual Wmax.[8] Similar physiologic training effects have also been reported by

others.[7] In the present study, the improvement in performance during maximal incremental cycle exercise was achieved at a similar peak VO_2, HR and change in base excess. Peak $\dot{V}O_2$ improved by more than 10% in four patients, but base excess remained unchanged. No measurements were obtained at iso work rate after training, which may have concealed some effects of training. Furthermore, cycling exercise was only a component of the training programme. These results suggest, that the effects of training were mainly achieved by an improvement in exercise efficiency. Indeed, Wmax/peak HR and Wmax/peak VO_2 increased by 0.1 W/(beats/min) (p=0.1) and 8.1 W/(L/min) (p=0.1), respectively, but these changes did not reach significance. The Borg score at peak exercise did not change, which indicates some adaptation to dyspnoea.

We conclude that patients with severe COPD can achieve high exercise intensities during training in relation to individual maximum exercise values. Pulmonary rehabilitation, including exercise training, improved maximum exercise performance.

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CHAPTER 4

Ventilatory response to positive and negative work in patients with chronic obstructive pulmonary disease

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4.1 Abstract

Study objective – In healthy subjects, oxygen consumption and cardiorespiratory responses are lower during eccentric exercise (negative work, Wneg) than during concentric exercise (positive work, Wpos) at the same work load The aim of the present study was to investigate the ventilatory response to Wneg in patients with chronic obstructive pulmonary disease (COPD)
Patients and methods – Twelve subjects with COPD (FEV_1 mean (SD) 1 5 (0 4) L, 46 (16) % of predicted) performed concentric and eccentric exercise tests (6 min of exercise, interval ≥ 1h) in random order at constant work loads of 25% and 50% of the individual maximal (positive) work capacity
Results – VE, VO_2 and VCO_2 were 30% lower during Wneg than during Wpos for both work intensities The breathing reserve during 25%Wneg was 11 (8) % and during 50%Wneg 18 (14) % higher than during Wpos at corresponding work loads ($p<0$ 01) VE/VO_2 and VE/VCO_2 were similar during Wpos and Wneg $PaCO_2$ increased by 0 1 (0 4) kPa during 50%Wneg and by 0 7 (0 5) kPa during 50%Wpos ($p<0$ 01) During 50%Wneg perceived leg effort (modified Borg scale) tended to be higher than perceived breathlessness (2 4 (1 2) versus 2 0 (1 1)
Conclusions – In subjects with COPD the ventilatory requirements of Wneg were considerably lower than those of Wpos at similar work loads up to 50% of maximal work capacity During Wneg the ventilatory reserve was higher and gas exchange was less disturbed as a result of a lower VO_2 and VCO_2

4.2 Introduction

Dynamic work is performed either as concentric (positive work, Wpos) or as eccentric (negative work, Wneg) exercise Both types of exercise are used during many activities of daily life During Wpos (lifting a weight, walking upstairs) the contracting muscle shortens During Wneg the muscle, while contracting, lenghthens in a controlled way.[1] Wneg is performed when walking downstairs or when lowering a weight to the floor.

In healthy subjects the oxygen cost of Wneg is lower than that of Wpos, as higher forces can be generated during Wneg [1] At similar work loads, electromyographic (EMG) activity is lower during Wneg as compared with Wpos, because fewer motor units are activated [2] This is accompanied with a lower cardiocirculatory and ventilatory response as well as a lower score for perceived exertion during Wneg [1 3 9]

Little attention has been paid to Wneg in patients who have a limited ventilatory reserve during exercise In patients with chronic obstructive pulmonary disease (COPD) the airway obstruction, the loss of elastic recoil, a diffusion limitation and ventilation to perfusion inequality lead to dyspnoea and abnormalities in gas exchange during exercise [10] As a result, they are unable to exert their peripheral muscles and have a reduced exercise tolerance. If the ventilatory load during Wneg would be substantially lower in patients with COPD, it might be a useful part of a training program in these patients However, it is not evident that the ventilatory response to Wneg is equally reduced in patients with COPD and in normal subjects. In patients with COPD, the ventilatory requirement during exercise is increased [10] Even at rest the ventilatory load may be increased by hypermetabolism and by the increased work of breathing.[11] Moreover, in healthy subjects, the differences between Wpos and Wneg became less at lower work loads.[2 4 8 9]

The aim of this study was to investigate the metabolic cost and ventilatory requirements of Wneg in comparison with Wpos in patients with COPD. Therefore, we studied the ventilatory and subjective responses to Wpos and Wneg at submaximal constant work loads in 12 patients with COPD

4.3 Methods

Study population

Twelve subjects (10 male) with COPD according to ATS criteria[12], who were referred to our centre for pulmonary rehabilitation, participated in the study. They had moderate to severe airway obstruction, and most of the subjects had signs of hyperinflation and a reduced diffusion capacity for carbon monoxide (Table 4.1). In each subject, reversibility of FEV_1 was less than 15% after inhalation of 400 μg

Table 4 1 Patient characteristics

Patients, *n*	12
Age, *yr*	56±12
Height, *m*	1 75±0 08
Weight, *kg*	73±8
TLC %predicted, *%*	100±18
FRC %predicted, *%*	118±27
RV %predicted, *%*	133±35
IVC %predicted, *%*	89±21
FEV_1, *L*	1 5±0 4
FEV_1 %predicted, *%*	46±16
KCO %predicted, *%*	55±25
PaO_2, *kPa*	10 1±1 4
$PaCO_2$, *kPa*	5 1±0 5

Values are presented as mean±SD Reference values were derived from Quanjer [13] TLC total lung capacity (He-dilution), FRC functional residual capacity, RV residual volume, IVC inspiratory vital capacity, FEV_1 forced expiratory volume in one second, KCO transfer coefficient for carbon monoxide (single-breath), PaO_2 arterial oxygen tension, $PaCO_2$ arterial carbon dioxide tension

salbutamol All subjects used inhaled beta-adrenergics and corticosteroids, 8 of them used oral theophylline and 2 used 10 mg per day oral prednisone They were all non- or exsmokers They had no exacerbations for at least 8 weeks and were familiar with the procedures of exercise testing The subjects had no neuromuscular or cardiovascular disease and a normal ECG Informed consent was obtained from each patient The study was approved by the hospital ethics committee.

Exercise protocol and measurements

Exercise was performed at a pedalling rate of 60 RPM on an electrically-braked cycle ergometer (Lode, Groningen, The Netherlands), which had been adapted for positive and negative work (Figure 4 1) [14] In the latter situation, the pedals were rotated in the backward direction by an electric motor at a rate of 60 RPM The electromagnetic brake of the ergometer was set at 25% or 50% of the individual maximal positive work load (maxWpos) The motor had to generate the same power to overcome this resistance During this procedure, the subjects were asked to let their legs be moved passively Subsequently, the electric brake was withdrawn and the subjects were instructed to brake the speed of the pedals and to maintain a backward pedalling rate of 60 RPM From that moment, the power generated by the motor to overcome the resistance of the electric brake was absorbed by the patient, who then performed Wneg at an equivalent load

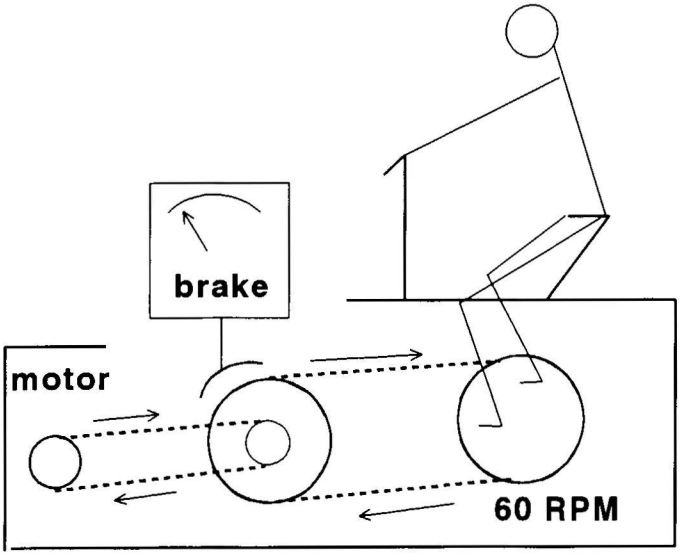

Figure 4.1. Schematic presentation of a cycle ergometer for eccentric exercise. The pedals are driven in backward direction at a rate of 60 RPM by the electric motor, which has to overcome the adjustable resistance of the electromagnetic brake. After withdrawal of the brake, the subject has to maintain a backward pedalling rate of 60 RPM by braking the speed of the pedals.

As it is not a common activity, the physiological response to Wneg depends on the skill involved in performing eccentric cycling exercise.[4] Furthermore, Wneg is associated with delayed muscle soreness and muscle damage, but adaptation may occur after a repeated bout of the same exercise at a low intensity and of short duration.[15] Therefore, the subjects performed eccentric exercise at work loads between 50 and 100% of maxWpos, 2 to 4 weeks before the start of the study.

Arterial blood samples were drawn from an indwelling catheter in the brachial artery at rest, at the end of exercise and after 3 min of recovery, and they were analysed immediately (Ciba Corning 178 DMS, Houten, The Netherlands). Heart rate (HR) was monitored by one lead ECG recording. The predicted maximal heart rate was calculated by 220 minus age.[16] Minute ventilation ($\dot{V}E$), oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured every 30 s by a mixing chamber ergospirometry unit (Oxycon IV, Mijnhardt, Maarsen, The Netherlands). Maximal exercise ventilation was predicted by the formula: predicted $\dot{V}E$max = 37,5 x FEV_1.[17] Breathing reserve was calculated by [1 – $\dot{V}E/\dot{V}E$max pred.] x 100%). The dead space/tidal volume ratio (VD/VT) was calculated by means of the Bohr equation. At the end of the test, perceived exertion was scored for breathlessness and for leg effort, on a modified Borg scale (range 0-10).[18]

Maximal incremental exercise test

Four to 6 weeks before the start of the study, a symptom-limited incremental (concentric) exercise test was performed. The subjects cycled at a pedalling rate of 60 RPM breathing ambient air. The work rate was increased each minute by 10% of the predicted maximal work load until exhaustion.[19] All subjects stopped because of dyspnoea. Mean (SD) maximal work load (maxWpos) was 88 (29) W (range 30-135 W), mean VO_2max was 1 3 (0 3) L/min (Table 4.2). $PaCO_2$ rose by 0 6 kPa from rest to maximum, indicating a ventilatory limitation. Three subjects were hypoxic (PaO_2 <7.3 kPa) at maximum. Base excess decreased by more than 4 mmol/L in all but one subject (Table 4 2), suggesting that work was performed above the anaerobic threshold.[16]

Table 4 2 Maximal incremental exercise test

maxWpos, *W*	88±29
Peak HR, *beats/min*	141±26
Peak HR %HRmax pred , *%*	87±17
Peak VE, *L*	45±13
Peak VE %VEmax pred , *%*	82±19
VO_2max, *L/min*	1 3±0 3
VCO_2max, *L/min*	1 3±0 3
PaO_2, *kPa*	9 1±2 2
$PaCO_2$, *kPa*	5 7±1 0
Δbase excess, *mmol/L*	-6 3±1 9
Dyspnoea, *Borg scale*	6 0±2 0
Leg effort, *Borg scale*	5 8±1 8

Values are presented as mean±SD MaxWpos maximal (positive) work load, HR heart rate, VE minute ventilation, VO_2 oxygen consumption, VCO_2 carbon dioxide production, Δbase excess change in base excess For further definitions see legend to Table 4 1

Single-stage concentric and eccentric exercise tests

Four single-stage exercise tests were performed in random order on 2 consecutive days with a maximum of 2 tests on the same day. All subjects inhaled 400 μg salbutamol 2 h before the first exercise test of each day. FEV_1 varied less than 10% from the value measured previously. The second exercise test was performed after a resting period of at least 1 h. The subjects cycled both concentrically and eccentrically for 6 min at constant work loads of 25% and 50% of their individual maxWpos.

Statistical analysis

The results were expressed as mean values (standard deviation, SD). Differences between Wneg and Wpos at corresponding work levels were compared by means

of the Wilcoxon test for paired samples and corrected for multiple measurements. The level of significance was set at a p-value less than 0.01.

4.4 Results

All subjects could sustain exercise for 6 min during all tests, and no significant decrease in base excess occurred. HR and $\dot{V}E$ did not reach predicted maximal values. The highest VO_2 (0.85 (0.14), range 0.7-1.1 L/min) was achieved during 50%Wpos. $\dot{V}E$, VO_2 and VCO_2 were approximately 30% lower during Wneg than during Wpos for both work intensities. The breathing reserve during 25% Wneg was 11 (8) % and during 50%Wneg 18 (14) % higher (Table 4.3, Figure 4.2).

Table 4.3 Exercise responses to positive (Wpos) and negative work (Wneg) at 25% and 50% of maximal positive work capacity (maxWpos)

	25% of maxWpos		50% of maxWpos	
	Wpos	Wneg	Wpos	Wneg
Work load, *W*	22±7		44±14	
HR, *beats/min*	95±16	84±17	98±13	92±14
HR %HRmax pred., *%*	58±8	53±12	64±6	57±11
VE, *L/min*	22±3	16±4*	29±6	19±7*
VE %VEmax pred., *%*	42±15	31±12*	55±14	37±16*
Breathing reserve, *%*	58±15	69±12*	45±14	63±16*
VO_2, *L/min*	0.65±0.06	0 45±0.07*	0.85±0.14	0.54±0.10*
VCO_2, *L/min*	0.58±0.06	0.38±0.07*	0 83±0.13	0.49±0.14*
VE/VO_2	33.3±5.3	34.8±5.5	34.7±4.7	34.1±7.2
VE/VCO_2	36.8±4.5	41.5±6.2	35.4±4.0	38.6±5.5
O_2 pulse, *ml O_2/beat*	6.8±1.2	5.2±0.7*	8.1±1.1	5.9±1.2*
PaO_2, *kPa*	9.8±1.6	9.9±1.7	9.8±2.1	10.2±1.5
$PaCO_2$, *kPa*	5.3±0.5	5.1±0 5	5.3±0.8	5.1±0.6
ΔPaCO2, *kPa*	0 6±0.6	0.4±0.4	0.7±0 5	0.1±0.4*
Δbase excess, *mmol/L*	0.7±1.6	0.6±0.6	-0.3±1.3	0.4±1.0
VD/VT	0.34±0.09	0 39±0.12	0.34±0.08	0.35±0.13
Dyspnoea, *Borg scale*	2.0±1.1	1.4±0.9	2.7±1.0	2.0±1.1
Leg effort, *Borg scale*	1.5±1.0	1 3±1.1	1.8±1.3	2.4±1.2

Values are presented as mean±SD. VE/VO_2: ventilatory equivalent for oxygen; VE/VCO_2: ventilatory equivalent for carbon dioxide; ΔPaCO2; change in $PaCO_2$; VD/VT: dead space/tidal volume ratio. For further definitions see legends to Tables 4.1 and 4.2.

*$p<0.01$: comparison between Wpos and Wneg for corresponding work loads.

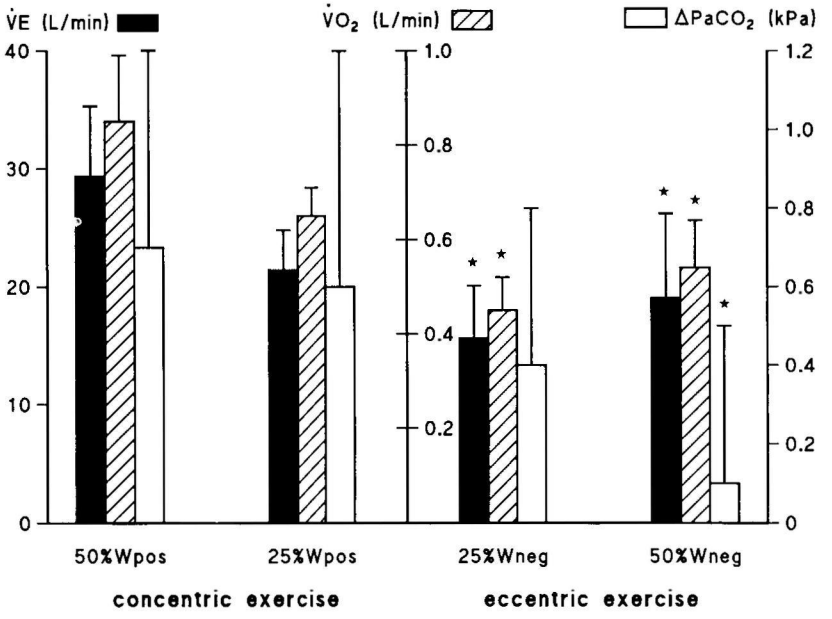

Figure 4.2. Mean minute ventilation ($\dot{V}E$, solid bars), oxygen consumption ($\dot{V}O_2$, hatched bars) and change in $PaCO_2$ ($\Delta PaCO_2$, open bars) in 12 subjects with COPD after 6 min of positive (Wpos) and negative work (Wneg) at 25% and 50% of maximal (positive) work load. Error bars represent standard deviation.
*$p<0.01$: comparison between Wpos and Wneg for corresponding work loads.

The ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) and for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) did not differ significantly between Wpos and Wneg. No significant differences occurred in VD/VT between the two types of work at either work load. The increase of $PaCO_2$ during 50%Wneg was significantly less than during 50%Wpos (0.1 versus 0.7 kPa, $p<0.01$) (Figure 4.2). Two out of 3 subjects, who were hypoxic at maxWpos, had a PaO_2 of 6.2 kPa during 50%Wpos, whereas during 50%Wneg PaO_2 did not fall below 8.1 kPa.

Differences in heart rate between Wpos and Wneg were small, but for any given $\dot{V}O_2$ the heart rate was higher during Wneg. In consequence, oxygen pulse ($\dot{V}O_2/HR$) was significantly lower during Wneg than during Wpos.

The scores for perceived breathlessness and leg effort were less during single-stage exercise than during maximal incremental exercise. The sensation of dyspnoea was less during Wneg than during Wpos, and leg effort scored higher during 50%Wneg than during 50%Wpos, but the differences between Wpos and Wneg were not significant.

4.5 Discussion

This study in patients with COPD showed that VE, VO_2 and VCO_2 during Wneg were 30% lower than during Wpos at similar work loads of 22 and 44 W. As a result, the patients had a greater ventilatory reserve during Wneg.

In normal subjects performing steady-state exercise at equal work loads above 100 W, VE and VO_2 during Wneg were 50-70% lower than during Wpos At lower work loads the differences in VE and VO_2 between Wpos and Wneg were smaller.[1 3 4 8 9] This may be explained by the extra work performed during eccentric cycling by the muscles of the trunk and of the upper extremities to stabilize the body This unmeasured work will be relatively high at low external work loads.[8] In addition, Aura and Komi have shown that the mechanical efficiency during Wneg, defined as the ratio of the output to the input energy, was positively correlated with work intensity [20] In our patients with COPD decreased work of breathing may have contributed to the reduced oxygen cost of Wneg.

Knuttgen et al found a higher ventilatory equivalent for oxygen (VE/VO_2) during eccentric exercise than during concentric exercise at similar work loads [4] The authors suggested a different mechanoreceptor activity or motor activity during Wneg. This was not supported by others, who found that VE and VO_2 were proportionnally reduced.[5 8 9] VE appeared to be more closely correlated with VCO_2.[8 21] We found no differences in VE/VO_2, VE/VCO_2 and dead space ventilation between Wpos and Wneg, and changes in base excess were negligible. Therefore, we believe that an absolute reduction in VO_2 and VCO_2, and a greater ventilatory reserve rather than an increased ventilatory drive or improved alveolar ventilation, explain the improvements in gas-exchange during Wneg in contrast to Wpos.

Data about the cardiocirculatory response to Wneg in normal subjects are contradictory. In most studies, the heart rate during Wneg was lower than during Wpos at similar work loads [4 6 8 9] In contrast, during maximal leg extension, a higher heart rate and cardiac output has been found during the eccentric than during the concentric phase of exercise.[22] When Wpos was compared with Wneg at equal levels of VO_2 below 1 L/min, the heart rate was higher during Wneg[7 8 21], whereas the cardiac output was the same[5 7]. In the present study, differences in HR were not significant between Wpos and Wneg at similar work loads, but oxygen pulse (VO_2/HR) was lower during Wneg. Therefore, we assume that the cardiocirculatory response to Wneg in patients with COPD is essentially the same as in normal subjects.

In normal subjects, the score for perceived exertion at a given work load was lower during Wneg than during Wpos, while for similar levels of VO_2, Wneg was experienced as more strenuous [6] In our study, the Borg scores for dyspnoea and perceived leg effort did not differ significantly between Wpos and Wneg, probably because the work loads were too low. However, during 50%Wneg perceived leg

effort scored higher than perceived breathlessness, which is in agreement with the reduced ventilatory load and greater ventilatory reserve at this work level Thus, Wneg resulted in a subjective response which was quite similar to what has been found in normal subjects

Work loads above 50% of maxWposWe were not used in the present study for several reasons Firstly, in patients with COPD, the ventilatory requirements might have exceeded the ventilatory capacity at higher work loads This would have concealed differences in exercise response between Wpos and Wneg Secondly, Wneg is associated with delayed-onset muscle soreness and muscle damage resulting in loss of muscle strength [23 27] This might be more pronounced in the elderly because of a smaller muscle mass and a lower VO_2max.[28] The present subjects were in a moderate physical condition, untrained and not accustomed to performing heavy exercise For this reason, they had performed eccentric exercise at least two weeks before the tests to induce adaptation and to prevent muscle damage at the time of the tests [15 25]

Both muscular tension and metabolic cost are stimuli which may increase muscle strength [29] In normal subjects, eccentric exercise have shown to provide a stimulus to gain static and dynamic muscle strength, and has been used in many training programmes [29 33] This was also found in an old age group [34] The results of the present study warrant further investigation into whether patients with COPD may benefit from eccentric exercise training during pulmonary rehabilitation The reduced ventilatory load during Wneg might enable these patients to train their peripheral muscles at a higher external work load and for a longer duration than during Wpos If so, the increased muscular tension and total amount of work during eccentric exercise training would enhance the effects of conventional training programmes

We conclude that in patients with COPD the ventilatory requirements of eccentric exercise were considerably lower than those of concentric exercise at similar work loads up to 50% of the individual maximal work capacity As a result, the ventilatory reserve was greater and gas exchange was less disturbed during Wneg than during Wpos in these patients

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CHAPTER 5

Potassium and ventilation during positive and negative work in patients with chronic obstructive pulmonary disease

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5.1 Abstract

Study objective – In patients with chronic obstructive pulmonary disease (COPD) reduced ventilatory reserves limit exercise tolerance. In these patients, the ventilatory requirements of eccentric exercise (negative work, Wneg) are lower than those of concentric exercise (positive work, Wpos) at similar work loads. In this study, we investigated the relationship between plasma potassium levels and ventilation during Wpos and Wneg in these patients

Patients and methods – Twelve patients with stable COPD (mean (SD) FEV_1 46 (16) % of predicted) performed Wpos and Wneg on a cycle ergometer (6 min of exercise; interval ≥ 1 h) in a randomized order at a constant work load of 50% of the individual maximum (positive) work capacity. Minute ventilation (VE) and arterial plasma potassium concentration ($[K^+]a$) were measured at rest, and at 1-minute intervals during exercise and during 3 min of recovery.

Results – VE increased less during Wneg in comparison with Wpos (6 [range 3-26] versus 18 [range 8-28] L/min, $p<0.01$) VE during Wneg was reduced in proportion to VCO_2. The increase in $[K^+]a$ during Wpos and Wneg (0.45 [range 0.26-0.75] and 0.34 [range 0.1-0 97] mM) did not differ significantly. VE was closely correlated with VCO_2 during both types of exercise. VE was also closely correlated with $[K^+]a$, but the slope of the relationship between $[K^+]a$ and VE was steeper during Wpos than during Wneg (39.1 [range 15 2-88 6] versus 18.3 [range 7.2-37.3] L min^{-1} mM^{-1}, $p=0.012$). In contrast, the slope of the relationship between VCO_2 and VE was similar during both types of exercise (27.8 [range 19.2-37.1] versus 32.1 [range 19.8-48.4]) Thus, for a given increase in $[K^+]a$, the increase in VE was significantly less during Wneg.

Conclusions – In patients with COPD, potassium did not explain the difference in exercise ventilation between Wneg and Wpos, and may not play a significant role in the control of breathing during low-intensity exercise.

5.2 Introduction

Ventilation during exercise is controlled by a complex interaction of neural and humoral drives Recently, potassium has received attention as a stimulus of ventilation [1] Potassium is released during exercise from the intracellular stores of the contracting muscles in proportion to the exercise intensity [2,3] In normal subjects, VE and VCO_2 show a close temporal relationship with arterial plasma potassium concentration ($[K^+]a$) during light and heavy dynamic exercise, suggesting that potassium is one of the factors which contribute to the control of breathing during exercise [4,6]

In contrast to normal subjects, patients with chronic obstructive pulmonary disease (COPD) are ventilatory limited during exercise The reduced breathing capacity in these patients limits maximal work capacity During exercise at similar submaximal work rates, ventilation is higher in patients with COPD than in normal subjects due to impaired pulmonary mechanics [7] If potassium substantially contributes to the exercise hyperpnoea in patients with COPD, conditions that influence $[K^+]a$ may in this way have an effect on exercise tolerance Patients with COPD regularly use (inhaled) β_2-adrenergic drugs and corticosteroids, and may be treated with diuretics, all of which influence $[K^+]a$ Few studies have investigated the role of potassium in the exercise hyperpnoea in COPD A reduced ventilatory response in relation to $[K^+]a$ has been reported in patients with COPD compared with normal subjects [8] However, as maximal incremental exercise was performed, it was not clear whether this was caused by a reduced sensitivity to potassium or by the ventilatory impairment in the patients

Dynamic exercise can be performed as concentric (positive work, Wpos) or as eccentric (negative work, Wneg) exercise In healthy subjects, the metabolic cost and ventilatory requirements of eccentric exercise are 30-50% lower than those of concentric exercise at similar work loads [9-13] Therefore, Wneg might be a suitable type of exercise and training in patients with limited ventilatory reserves Indeed we have previously found that the ventilatory response to eccentric exercise was also reduced in patients with COPD [14]

The aim of the present study was to investigate whether potassium contributes in a clinically relevant way to exercise hyperpnoea in patients with COPD For this purpose we studied the relationship between $[K^+]a$ and VE during concentric and eccentric exercise at submaximal work loads We hypothesized that if $[K^+]a$ is a prominent factor among the many stimuli which control exercise hyperpnoea, the relationship between $[K^+]a$ and VE will be independent of the type of work Thus, we expected that the lower exercise ventilation during Wneg would be accompanied by similarly decreased levels of $[K^+]a$

5.3 Methods

Study population

Twelve patients (10 male) with COPD according to ATS criteria[15], who were referred to our centre for pulmonary rehabilitation, participated in the study. They had moderate to severe airway obstruction, most of them with signs of hyperinflation and a reduced diffusion capacity for carbon monoxide. The characteristics are summarized in Table 5 1 All patients used inhaled β_2-adrenergic drugs and corticosteroids, 8 of them used oral theophylline and 2 used oral prednisone in doses of 10 mg per day All patients were ex-smokers. They had been in a stable clinical condition for at least 8 weeks and were familiar with the procedures of exercise testing The patients had no neuromuscular or cardiovascular disease and a normal ECG Informed consent was obtained from each patient The study was approved by the hospital ethics committee

Table 5 1 – Patient characteristics

Patients, *n*	12
Age, *yr*	56±12
Height, *m*	1 75±0 08
Weight, *kg*	73±8
TLC %predicted, *%*	100±18
FRC %predicted, *%*	117±18
FRC %TLC, *%*	59±8
IVC %predicted, *%*	89±21
FEV_1, *L*	1 5±0 4
FEV_1 %predicted, *%*	46±16
K_{CO} %predicted, *%*	55±25

Values are presented as mean±SD Reference values derived from Quanjer [16] TLC total lung capacity (He-dilution), FRC functional residual capacity, IVC inspiratory vital capacity, FEV_1 forced expiratory volume in one second, K_{CO} transfer coefficient for carbon monoxide (single breath)

Exercise protocol and measurements

Exercise was performed at a pedalling rate of 60 RPM on an electrically-braked cycle ergometer, which had been adapted for positive and negative work (Lode, Groningen The Netherlands) [17] Maximum (positive) work capacity (maxWpos) had been determined previously during a symptom-limited maximal incremental cycle exercise test The work rate was increased at 1-minute intervals by 10% of predicted maxWpos [18]

During eccentric cycling the pedals were driven in backward direction by an electric motor at a rate of 60 RPM The electromagnetic brake of the ergometer

was set at 50% of the individual maxWpos The motor had to generate the same power to overcome this resistance. During this procedure, the subjects were asked to let their legs be moved passively Subsequently, the electric brake was withdrawn and the subjects were instructed to brake the speed of the pedals and to maintain a backward pedalling rate of 60 RPM. The amount of energy generated by the motor to overcome the resistance of the electric brake, was now absorbed by the patient, who thus performed Wneg at an equivalent load

Wneg is associated with delayed muscle soreness and muscle damage, but adaptation may occur after a repeated bout of the same exercise at a low intensity and of short duration.[19] For this reason, and to acquaint the patients with Wneg, repeated bouts of eccentric exercise at work loads between 50% and 100% of maxWpos had been performed 2-4 weeks before the start of the study.

Two single-stage exercise tests at a constant work load of 50% maxWpos were performed The patients cycled both concentrically and eccentrically for 6 min in a randomized order with periods of rest of at least 1 h. They had inhaled 400 µg salbutamol 2 h before the tests Arterial blood was drawn from an indwelling catheter in the brachial artery at rest and at 1-minute intervals during 6 min of exercise and during 3 min of recovery. Samples (5 ml) were collected in heparinized syringes, centrifuged and analysed for $[K^+]a$ by flame photometry (Instrumentation Laboratory 943, IJsselstein, The Netherlands). Resting $[K^+]a$ was taken as the mean of two measurements Samples for blood gas analysis were collected separately in heparinized syringes at rest, at 3 min intervals during exercise and after 3 min of recovery, and they were analysed immediately (Ciba Corning 178 DMS, Houten, The Netherlands) Heart rate was monitored by one-lead ECG recording VE, VO_2 and VCO_2 were measured by a mixing chamber ergospirometry unit (Oxycon IV, Mijnhardt, Maarssen, The Netherlands) Mean values over periods of 30 s preceding each $[K^+]a$ sample were registered. Predicted maximal exercise ventilation was calculated by the equation predicted VEmax = FEV_1 x 37,5.[20]

Statistical analysis

The results were expressed as median (range) values and where appropriate as mean values (standard deviation, SD). Changes during exercise and differences between Wneg and Wpos were compared with the Wilcoxon test for paired samples Relationships between various parameters were assessed by the Spearman correlation coefficient. The level of significance was set at a p-value less than 0 05

5.4 Results

Exercise response to Wpos and Wneg

All 12 patients could sustain concentric and eccentric exercise for 6 min at a constant work load of 50% of maxWpos (44 W, range 20-65 W) (Table 5.2).

Table 5.2 Exercise response to positive (Wpos) and negative work (Wneg) at a constant work load of 50% of maxWpos (44±14 W) on a cycle ergometer

	Wpos			Wneg		
	Rest	Exercise	Recovery	Rest	Exercise	Recovery
VE, *L/min*	11 (5-19)	30 (19-39)	15 (6-24)	11 (7-16)	17 (12-36)**	11 (5-24)**
$[K^+]a$, *mM*	4 14 (3 77-4.73)	4.59 (4 30-5 08)	4 33 (4 00-4 97)	4.11 (3.83-4 58)	4.45 (4 03-5.35)	4.35 (3.83-4.72)
VO_2, *L/min*	0.29 (0.13-0.41)	0.83 (0 68-1 14)	0 30 (0 15-0 47)	0.28 (0.15-0.40)	0.52 (0 37-0.73)**	0.28 (0.22-0.37)
VCO_2, *L/min*	0.27 (0 12-0.39)	0.82 (0.65-1 06)	0 32 (0 16-0.51)	0.24 (0.13-0.37)	0 44 (0 33-0.78)**	0.27 (0.12-0 42)
HR, *beats/min*	79 (61-98)	99 (84-119)	83 (64-100)	81 (62-105)	90 (72-142)	81 (62-112)
Base-excess, *mM/L*	0.3 (-2.5- 4.6)	0.5 (-2.3- 2.6)	0.1 (-2.4- 3.2)	0.2 (-1.9- 2.9)	0 5 (-1.4- 4.8)	0 4 (-2 7- 4.3)
pHa	7.44 (7 40-7.49)	7.41 (7.33-7.43)	7.44 (7 37-7.46)	7.42 (7.38-7.45)**	7.42 (7.37-7 43)	7 42 (7.37-7.47)
PaO_2, *kPa*	10.6 (8.4-12 9)	10.0 (6.2-13.1)	11 8 (9.0-14.3)	10 6 (7 7-12.8)	10 3 (7 5-12.4)	10 6 (6.1-14.0)**
$PaCO_2$, *kPa*	4 7 (3.9-5 2)	5 1 (4 3-7.0)	4.7 (3.9-6 2)	5.0 (4.1-5.7)*	4 9 (4.3-6.1)	4.9 (4.4-6 6)**

Values are presented as median (range). MaxWpos: maximal (positive) work load; VE minute ventilation; $[K^+]a$ arterial plasma potassium concentration; VO_2: oxygen consumption; VCO_2 carbon dioxide production, HR: heart rate; PaO_2: arterial oxygen tension, $PaCO_2$ arterial carbon dioxide tension *p<0 05, **p<0.01: comparison between Wpos and Wneg.

At rest before Wneg, pHa was lower and $PaCO_2$ was higher than resting values before Wpos. Resting VE and $[K^+]a$ were similar before both types of exercise.

After 6 min of exercise, VE, $\dot{V}O_2$ and $\dot{V}CO_2$ were 40% lower during Wneg than during Wpos ($p<0.01$). $\dot{V}E$ during Wpos was 58 (range 31-85)% and during Wneg 34 (range 15-68)% of predicted $\dot{V}E$. There was no significant difference in $[K^+]a$ between Wpos and Wneg. The patients achieved similar levels of heart rate, pHa, base-excess, PaO_2 and $PaCO_2$ during both types of exercise. Resting $PaCO_2$ was higher, but the increase in $PaCO_2$ during Wneg was less than during Wpos (-0.1 versus 0.4 kPa; $p<0.01$).

After 3 min of recovery from Wneg, VE and PaO_2 were lower and $PaCO_2$ was higher than after recovery from Wpos.

Time courses of $\dot{V}E$ and $[K^+]a$

The increases in VE and $[K^+]a$ during 6 min of exercise and 3 min of recovery are shown in Figure 5.1. During both types of exercise, $\dot{V}E$ did not reach a plateau. VE increased by 18 (range 8-28) L/min during Wpos and by 6 (range 3-26) L/min during Wneg (Wpos versus Wneg: $p<0.01$). The increase in $[K^+]a$ by 0.45 (range 0.26-0.75) mM and 0.34 (range 0.1-0.97) mM, respectively, did not differ significantly.

During 3 min of recovery from exercise, VE returned to resting values after Wneg, whereas $[K^+]a$ remained significantly elevated after both types of exercise ($p<0.01$).

Relationships between $[K^+]a$, VCO_2 and VE

The increase in $\dot{V}E$ during 6 min of exercise (ΔVE) was less during Wneg than during Wpos. The differences in $\Delta\dot{V}E$ between Wpos and Wneg [$\Delta\dot{V}E$(Wpos-Wneg)] closely correlated with ΔVCO_2(Wpos-Wneg) ($r=0.95$; $p=0.002$). No correlations were found between ΔVE(Wpos-Wneg) and $\Delta[K^+]a$(Wpos-Wneg) ($r=-0.22$), ΔPaO_2(Wpos-Wneg) ($r=-0.22$), $\Delta PaCO_2$(Wpos-Wneg) ($r=-0.14$), Δbase excess(Wpos-Wneg) ($r=0.10$) and ΔpHa(Wpos-Wneg) ($r=0.32$) (p=NS).

Figure 5.2 shows the relationship between $\dot{V}E$ and $[K^+]a$ during Wpos and Wneg in each individual. VE closely correlated with $[K^+]a$ during Wpos (mean $r=0.94$, range 0.81-0.99) and during Wneg (mean $r=0.76$, range 0.44-0.97). The relationships between $[K^+]a$ and VE during Wpos and Wneg were calculated for each individual using linear regression analysis. The mean slope was significantly steeper during Wpos than during Wneg (39.1 (range 15.2-88.6) versus 18.3 (range 7.2-37.3) L min^{-1} mM^{-1}; $p=0.012$). The intercept was also significantly different between Wpos and Wneg (-148 [range -350 to -48] versus -65 [range -150 to -18] L/min; $p=0.014$).

VE also closely correlated with VCO_2 during Wpos (mean $r=0.99$, range 0.9-0.99) and Wneg (mean $r=0.96$, range 0.85-0.99). The relationship between $\dot{V}CO_2$ and VE did not differ between the types of exercise. During Wpos and Wneg the slope was 27.8 (range 19.2-37.1) and 32.1 (range 19.8-48.4), and the intercept 4.2 (range 1.6-10.9) and 3.4 (range 0.2-5.7) L/min, respectively.

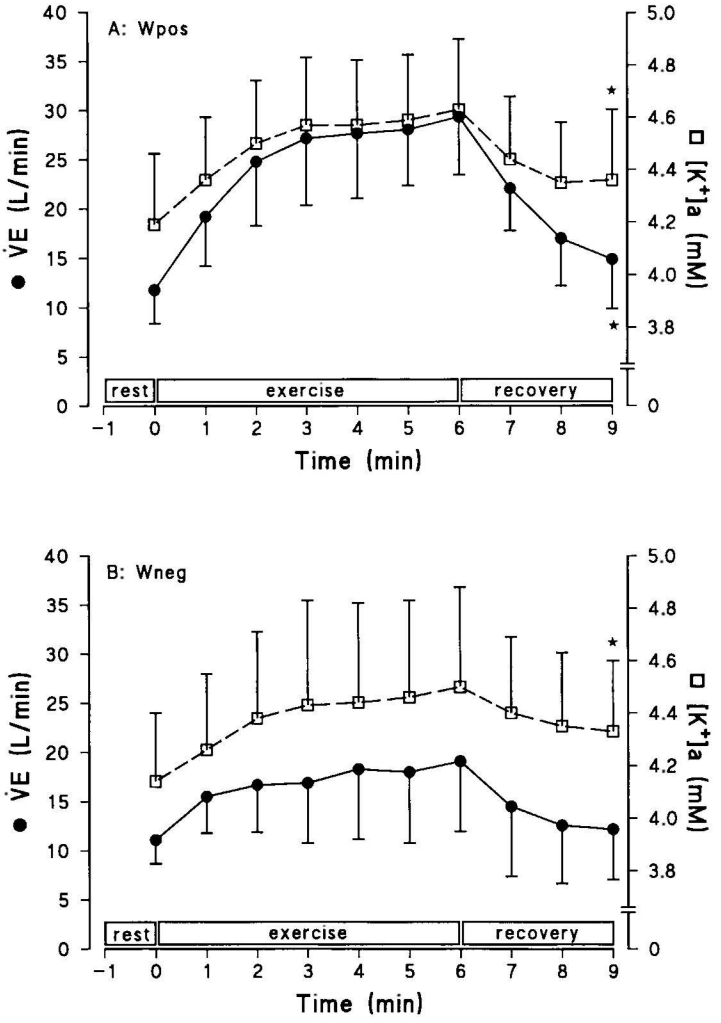

Figure 5.1. Time course of minute ventilation (V̇E: closed circles) and arterial plasma potassium concentration ([K⁺]a: open squares) during 6 min of cycle exercise at a constant work load of 50% of the individual maximum (positive work) load and during 3 min of recovery in 12 patients with COPD. The symbols represent mean values at each minute; error bars represent SD.

Panel A: positive work (Wpos); Panel B: negative work (Wneg).

*$p<0.01$: comparison between rest and at 3 min of recovery.

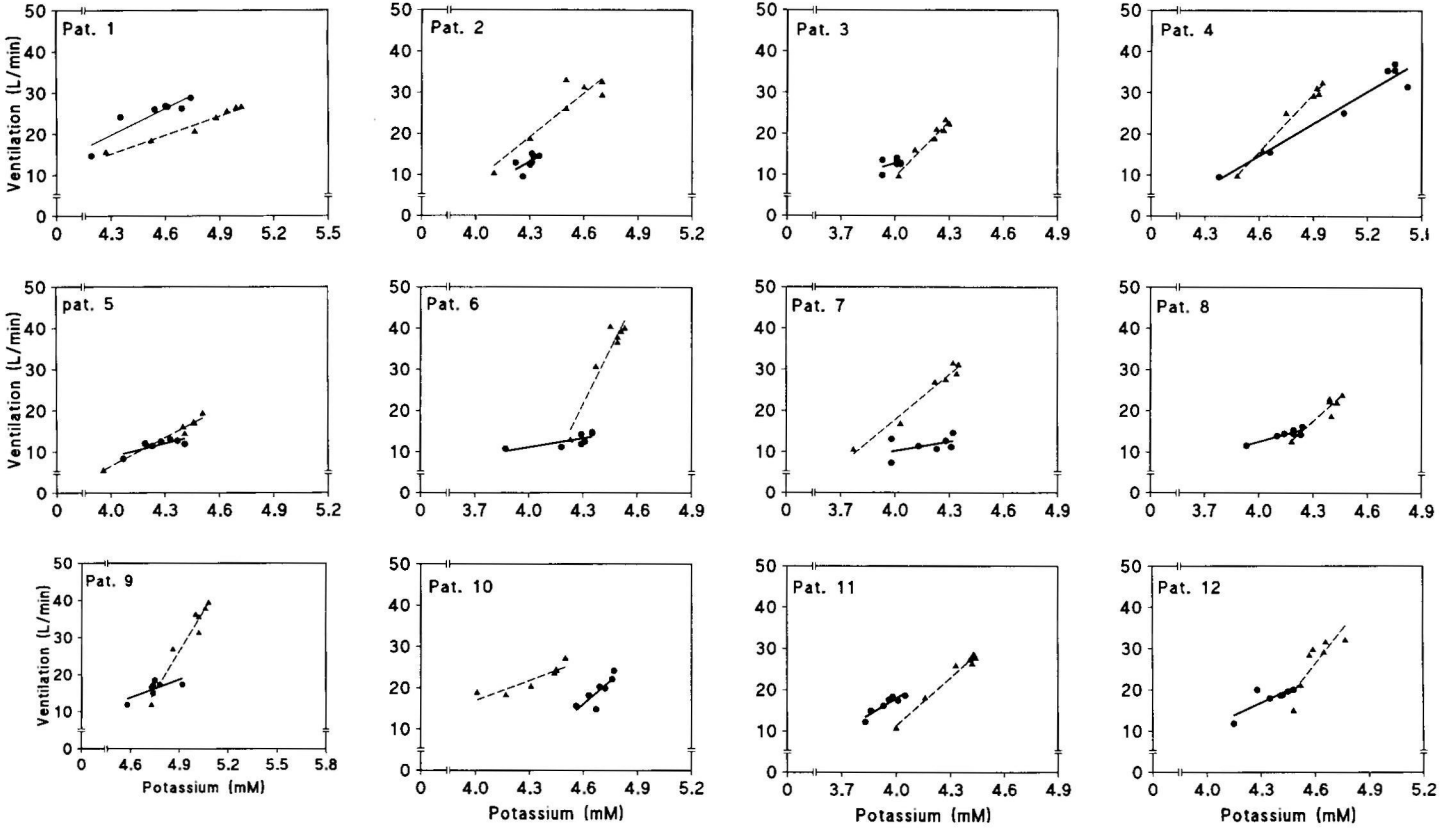

Figure 5.2. Relationship between arterial plasma potassium concentration ([K⁺]a) and minute ventilation (VE) during positive (closed triangles) and negative work (closed circles). The symbols represent the values at rest and at 1-minute intervals during 6 min of exercise. The straight lines are calculated by linear regression analysis. Each panel represents one patient.

5.5 Discussion

In this study, VE, VO_2 and VCO_2 were reduced by 40% during Wneg in comparison with Wpos at identical submaximal work loads. VE closely correlated with VCO_2 and the relationship between VCO_2, and VE was the same during both types of exercise. Although $[K^+]a$ also showed a linear relationship with VE during Wpos and Wneg, for a given increase in $[K^+]a$ the increase in VE was significantly less during Wneg. Thus, $[K^+]a$ did not substantially contribute to the difference in ventilatory response between Wneg and Wpos

Potassium may act as a respiratory stimulant via the carotid body and via CIII and CIV afferents of the muscle [21 22] In the anaesthetized cat, an increase in $[K^+]a$ by 3 mM increased carotid chemoreceptor discharge and ventilation [22] The effect of increased levels of $[K^+]a$ on ventilation was enhanced by hypoxia and abolished by hyperoxia or surgical denervation of the peripheral arterial chemoreceptors [23 25] During exercise the sensitivity of the carotid bodies increases as a function of work rate. Metabolic acidosis and increases in $[K^+]a$, catecholamines and osmolarity may all contribute to the exercise hyperpnoea by stimulating the carotid body [26 27] The rise in $[K^+]a$ during exercise is the net result of potassium efflux and incomplete re-uptake via Na^+-K^+ ATP-ase in exercising and resting muscles [3 28] The close temporal relationship between $[K^+]a$ and VE during low and high intensity concentric exercise in normal subjects suggests that potassium may play a significant role in the exercise hyperpnoea.[4 6 29]

In a recent study, Yoshida et al.[8] reported a linear relationship between $[K^+]a$ and VE during maximal incremental cycle exercise in healthy subjects and patients with COPD. The slope of the VE to $[K^+]a$ relationship was significantly steeper in healthy subjects (37 (7) L min^{-1} mM^{-1}) than in patients with COPD (16 (7) L min^{-1} mM^{-1}) At maximum exercise, differences between healthy subjects and patients were observed in maximal work rate (245 versus 109 W), VE (70 versus 107% of predicted maximum), $PaCO_2$ (4 6 versus 6 4 kPa) and lactate (14.2 versus 4.8 mM).[8] Thus, the ventilatory limitation in patients with COPD may have accounted for the reduced exercise tolerance and for the lower slope of the VE to $[K^+]a$ relationship, as these patients were unable to raise ventilation in spite of increasing plasma potassium levels.

In the present study, VE during Wpos and Wneg was 58% and 34% of predicted maximum, respectively. The slope of the VE to $[K^+]a$ relationship during Wpos (39.1 L min^{-1} mM^{-1}) was in the same range as reported by Yoshida et al [8] in normal subjects. Differences in $[K^+]a$, PaO_2, $PaCO_2$, base-excess and pHa between Wpos and Wneg were small and did not explain the lower VE during Wneg. In contrast, VE closely mirrored VCO_2 during both types of exercise, suggesting that some receptor mechanism which senses changes in VO_2 and VCO_2 constitutes the major ventilatory drive during exercise, in this patient group also.

Due to the ventilatory impairment in the present patients, exercise at 50% of maximum work capacity corresponded with a work load of only 44 W As a result, increases in [K⁺]a were small [K⁺]a increased by less than 0 5 mM during both Wpos and Wneg whereas in the studies mentioned above [K⁺]a increased by 1-3 mM during exercise. It has previously been shown in healthy subjects that a 0 8 mM increase in [K⁺]a has little effect on ventilation during constant work load exercise (70 W) under normoxic conditions.[30] Therefore, the results of our study also suggest that in patients with COPD [K⁺]a may not be an important determinant of ventilatory drive during low-intensity exercise.

In the present study, the rise in [K⁺]a during Wneg was greater than expected for the metabolic rate in comparison with Wpos Mechanical force and increased heat production during eccentric exercise may cause muscle damage resulting in the release of muscle proteins (creatine kinase) [31] These factors may have contributed to extra loss and a delayed re-uptake of potassium during Wneg. As training enhances the re-uptake of potassium, the older age and the poor physical condition in the present patients may have delayed the normalization of [K⁺]a during the recovery from both types of exercise.[32]

High doses of inhaled β_2-adrenergics may induce hypokalaemia. Fifteen min after a cumulative dose of 800 μg salbutamol, [K⁺]a decreased by less than 0.1 mM.[33] We assumed that 400 μg salbutamol, inhaled 2 h before exercise, had not altered [K⁺]a in the present patients Moreover, possible effects would have occurred similarly during Wpos and Wneg.

We conclude that in patients with COPD potassium did not account for the difference in ventilatory response between Wneg and Wpos at similar levels of submaximal exercise.

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CHAPTER 6

Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise

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6.1 Abstract

Study objective – Supplemental oxygen has acute beneficial effects on exercise performance in patients with chronic obstructive pulmonary disease (COPD). The purpose of this study was to investigate the effects of training with supplemental oxygen in patients with severe COPD.
Patients and methods – We performed a randomized controlled trial in 24 patients with severe COPD who developed hypoxaemia during incremental cycle exercise (arterial oxygen saturation (SaO_2) < 90% at peak exercise) All patients participated in an in-patient pulmonary rehabilitation programme of 10 weeks duration. They were assigned either to general exercise training while breathing room air (GET/RA group: FEV_1 38% of predicted; PaO_2 10.5 kPa at rest; PaO_2 7.3 kPa at peak exercise), or to GET while breathing supplemental oxygen (GET/O_2 group: FEV_1 29% of predicted; PaO_2 10 2 kPa at rest; PaO_2 7.2 kPa at peak exercise) SaO_2 was not allowed to fall below 90% during the training. The effects on exercise performance while breathing air and oxygen, and on quality of life were compared.
Results – Maximum work load (Wmax) on room air significantly increased in the GET/RA group (mean (SD) 17 (15) W, $p<0.01$), but not in the GET/O_2 group (7 (25) W) Six min walking distance (6MWD), stair-climbing, weight-lifting exercise (all while breathing room air) and quality of life significantly increased in both groups. Training significantly increased Wmax, peak VCO_2 and 6MWD while breathing oxygen in both groups. Differences between groups were not significant
Conclusions – Pulmonary rehabilitation improved exercise performance and quality of life in both groups. Supplementation of oxygen during the training did not add to the effects of training on room air

6.2 Introduction

Hypoxaemia may occur during exercise in patients with chronic obstructive pulmonary disease (COPD). This is caused by alveolar hypoventilation, diffusion limitation, shunt, ventilation to perfusion inhomogeneity and a low mixed venous PO_2 (low cardiac output) [1] Exercise-induced hypoxaemia will raise the pulmonary artery pressure during exertion and may contribute to the decreased exercise tolerance in these patients [2]

Acute administration of supplemental oxygen has been shown to improve exercise performance in patients with COPD.[3-6] These acute effects of oxygen have been observed both in normoxic patients and patients who are hypoxaemic at rest or during exercise Several mechanisms may be involved, including reduction in ventilatory response to exercise (reduced ventilatory equivalent for carbon dioxide (VE/VCO_2))[6], ventilatory muscle recruitment[7] and delayed ventilatory muscle fatigue[8,9], improved aerobic capacity of the working muscles[10] and a reduction in breathlessness[11]

As a consequence, patients with COPD would be expected to benefit from supplemental oxygen during the training Indeed, recent guidelines recommend the administration of oxygen during exercise training in patients with exercise-induced hypoxaemia [12] Whether this approach results in a further improvement in exercise performance as compared to training on room air has not been fully clarified Many studies have investigated the effects of training in patients with COPD Some of these studies included a small number of patients who developed hypoxaemia during exercise and received supplemental oxygen during the training, whereas patients who did not desaturate trained on room air [13-15] Other, uncontrolled, studies have shown that oxygen-supplemented exercise training increased exercise performance [16,17] However, in these studies no comparison was made with a control training group breathing room air

We hypothesized that the administration of supplemental oxygen enables patients with COPD who develop hypoxaemia during exercise to achieve higher exercise intensities during the training. If so, this treatment might induce an additional physiologic training effect on the cardiocirculatory system and the peripheral muscles in terms of increased oxygen delivery, peripheral oxygen extraction and muscle oxygen utilization. As a result, training with supplemental oxygen might also enhance exercise performance on room air To test this hypothesis, we performed a controlled study to compare the effects of training with and without supplemental oxygen on exercise performance and quality of life in patients with severe COPD and hypoxaemia at peak exercise due to a diffusion-perfusion limitation

6.3 Methods

Study design and patients

Twenty-four patients with stable COPD[18], entered the study. All were referred to our hospital for pulmonary rehabilitation. They met the following inclusion criteria: hypoxaemia (arterial oxygen saturation (SaO_2) < 90%) at maximum exercise, and an increase in the alveolar-arterial difference in oxygen tension ($P(A\text{-}a)O_2$) of at least 2 kPa from rest to maximum exercise during maximal incremental cycle exercise. Patients were excluded if they had a resting PaO_2 of less than 8.5 kPa, a mean nocturnal SaO_2 of less than 90%, a mean pulmonary artery pressure (MPAP) of more than 25 mmHg measured at rest by Doppler echocardiography[19], and if they had neuromuscular or cardiovascular disease.

All patients were ex-smokers. Their medication was not changed during the study. They were familiar with the procedures of exercise testing. The patients were randomly allocated either to general exercise training while breathing room air (GET/RA), or GET while breathing supplemental oxygen (GET/O_2) at a flow rate of 4 L/min through a dual-prong nasal cannula. Informed consent was obtained from each patient. The study was approved by the hospital ethics committee.

Pulmonary rehabilitation programme

All patients participated in a multidisciplinary in-patient programme for 10 weeks, which consisted of physical training, breathing retraining, physical therapy (relaxation and mobilization exercises), education and psycho-social support.

General exercise training (GET)

Training consisted of dynamic and isometric strength training and specific training of daily life activities. Training sessions were held 5 days per week and had a mean duration of 80 min, including periods of rest.[20] GET comprised the following exercises: interval cycling (2 min of exercise alternated with 2 min of rest for 20 min); rowing (5 min); dynamic exercises for the muscles of the arm and shoulder-girdle using a pulley (5 min), and for the muscles of the back and abdomen by lifting the upper body and the legs, respectively, from the supine position (5 min); isometric strength training of the arms, shouldergirdles and legs (3 min); stair-climbing (3 min); sitting down and getting up from a chair alternated with slalom walking (5 min); and arm exercise by moving a weight of 1-2 kg between racks at 20 cm above and below shoulder level (5 min). All sessions were supervised by a physiotherapist. SaO_2 during exercise was monitored with a pulse oximeter using a finger probe (Oxyshuttle, Sensor Medics, Bilthoven, The Netherlands). Exercise training was started at low work loads. After the first week, the exercise intensity was gradually increased as tolerated by the patients.[21] In both groups, the work rate during the various exercises was not allowed to exceed the level at which SaO_2 fell below 90%.

Outcome measures

Pulmonary function tests

Spirometry and transfer coefficient for carbon monoxide (KCO, single breath) were performed according to European Respiratory Society (ERS) standards [22] All tests, including measurement of MPAP at rest, were repeated at the end of the training period

Maximal incremental cycle exercise test

The patients cycled on an electrically-braked cycle ergometer (Lode, Groningen, The Netherlands) at a pedalling rate of 60 revolutions per min (RPM), breathing room air The work rate was increased each min by 10% of the estimated maximal work load (Wmax) until exhaustion [23] Arterial blood samples were drawn from an indwelling catheter in the brachial artery Minute ventilation (VE), oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured every 30 s by a mixing chamber ergospirometry unit (Oxycon IV, Mijnhardt, Maarsen, The Netherlands) Breathlessness was scored every 3 min, and at the end of exercise, on a modified Borg scale [24] Peak VE was related to predicted maximal exercise values (VEmax predicted = 37 5 x FEV_1) [25]

Single-stage cycle exercise test

After 1 min of unloaded pedalling, exercise was performed at a constant work load of 65% of the actual Wmax Endurance cycling time was measured The test was terminated when the patient could not sustain exercise any longer, or after a maximum of 15 min The same measurements were made as during the maximal incremental test, except for bloodgas analysis

Activities of daily life

After 3 practise tests, the 6 min walking distance (6MWD) was measured in a gymnasium, while standardized encouragement was given [26 27] SaO_2 was measured continuously and breathlessness was scored at the end of the test

Stair-climbing was performed on an exercise staircase with a hand-rail, which had 4 steps for going up, a plateau, and 3 steps for going down The number of rounds during 5 min of exercise were counted

During weight-lifting the patients held a weight of 2 kg in the predominant hand and moved it between racks at 20 cm above and below shoulder level The number of lifts to both levels during 3 min was counted [28]

Acute effects of supplemental oxygen on exercise performance

The maximal incremental cycle exercise test, the single-stage exercise test and the 6MWD were repeated while oxygen was supplied at a flow rate of 4 L/min Resting periods between tests lasted at least 4 h During oxygen breathing it was not possible to measure VO_2, and blood gas analysis was not performed

Quality of life
Quality of life was assessed by means of the Chronic Respiratory Disease Questionnaire (CRDQ) [2] The questionnaire examines the dimensions dyspnoea, fatigue, emotional function and mastery Altogether 20 items are scored on a seven-point scale (maximum score 140 points, a higher score indicates a better quality of life) The test was administered at the start of the study and 6 weeks after completion of the pulmonary rehabilitation programme

Statistical analysis
The data were analysed with the Statistical Analysis System (SAS) package (SAS Institute Inc , Cary, NC, USA) The results were expressed as mean ± SD Changes within the training groups were compared with the Wilcoxon test for paired samples Differences between the groups were compared with the Kruskal Wallis test (Chi-square approximation) The correlation between various parameters was tested with the Spearman correlation coefficient Since multiple comparisons were performed the level of significance was set at a p-value less than 0 01

6.4 Results

Pulmonary function tests
The patients had severe airway obstruction and emphysema as suggested by hyperinflation They had a reduced KCO and an elevated resting $P(A\text{-}a)O_2$, but they were normoxic at rest Anthropometrics and resting pulmonary function remained unchanged after pulmonary rehabilitation No significant differences were present between groups (Table 6 1)

Cycle exercise intensity during the training
During the last 6 weeks of pulmonary rehabilitation, the mean (SD) work load achieved during interval cycle exercise training in the GET/RA and the GET/O_2 group was 114 (32)% and 124 (43)%, respectively, of Wmax during maximal incremental cycle exercise at the start of the study (GET/RA versus GET/O_2 p=0 12)

Exercise testing on room air
During *maximal incremental cycle exercise* before training, VE approached or exceeded predicted maximal values $PaCO_2$ increased by less than 1 kPa, while PaO_2 decreased and $P(A\text{-}a)O_2$ increased by approximately 3 kPa in both groups (Table 6 2) Training increased Wmax by 17 (15) W ($p<0$ 01) in the GET/RA group, and by 7 (25) W (p=0 1) in the GET/O_2 group Peak VE, VO_2, VCO_2 and the change in base excess (Δbase excess) were similar after training in both groups PaO_2

Table 6 1 Anthropometrics and resting pulmonary function before and after pulmonary rehabilitation

	GET/RA		GET/O_2	
	before	after	before	after
Patients, *n*	12		12	
Sex, *M/F*	10/2		10/2	
Age, *yrs*	59±13		63±5	
BMI, *kg/m²*	23 2±1 6	23 0±1 6	22 5±2 2	22 1±2 0
TLC %predicted, *%*	114±20	110±11	109±17	110±22
IVC %predicted, *%*	93±19	95±17	87±16	98±23
FEV_1, *L*	1 2±0 5	1 2±0 5	0 9±0 3	1 0±0 4
FEV_1 %predicted, *%*	38±11	38±12	29±7	33±9
KCO %predicted, *%*	37±14	40±15	30±14	30±15
MPAP, *mmHg*	13±3	16±7	17±7	15±5
PaO_2, *kPa*	10 5±1 1	10 2±1 3	10 2±1 6	9 5±2 0
$PaCO_2$, *kPa*	5 0±0 8	4 9±0 6	5 1±1 1	5 3±1 1
P(A-a)O_2, *kPa*	4 4±0 9	5 2±1 6	4 6±1 9	5 5±1 3

Values are presented as mean ± SD GET/RA general exercise training/room air, GET/O_2 general exercise training/supplemental oxygen M male, F female, BMI body mass index, TLC total lung capacity (He-dilution), IVC inspiratory vital capacity; FEV_1 forced expiratory volume in one second, KCO transfer coefficient for carbon monoxide (single breath), MPAP mean pulmonary artery pressure, PaO_2 arterial oxygen tension, $PaCO_2$ arterial carbon dioxide tension, P(A-a)O_2 alveolar-arterial difference in oxygen tension
No significant differences were present within and between groups

Table 6 2 Maximal incremental cycle exercise test breathing room air before and after pulmonary rehabilitation

	GET/RA		GET/O_2	
	before	after	before	after
Wmax, *W*	70±51	87±58*	58±33	65±39
Heart rate, *beats/min*	133±21	132±23	126±17	126±19
VE, *L/min*	43±21	43±21	35±15	37±17
VE %VEmax pred , *%*	96±23	95±18	101±23	92±13
VO_2, *L/min*	1 2±0 5	1 2±0 6	1 0±0 3	1 0±0 3
VCO_2, *L/min*	1 2±0 5	1 2±0 6	1 0±0 4	1 0±0 4
PaO_2, *kPa*	7 3±0 7	6 9±0 7	7 2±1 0	6 7±1 0*
$PaCO_2$, *kPa*	5 7±1 1	5 7±0 8	5 9±1 2	5 8±1 3
Δbase excess, *mmol/L*	-5 3±2 8	-5 7±2 8	-4 8±3.3	-5 4±3 4
P(A-a)O_2, *kPa*	7 7±1 3	8 2±1 5	7 4±1 3	8 1±1 5
Dyspnoea, *Borg scale*	7 3±2 4	5 8±1 9	6 6±2 1	5 3±1 2

Values are presented as mean ± SD Wmax maximum work load, VE minute ventilation, VO_2 oxygen consumption, VCO_2 carbon dioxide production, Δbase excess change in base excess For further definitions see legend to Table 6 1
*p<0 01 within-group comparison before versus after rehabilitation

at Wmax showed a further decrease after training in both groups, which was significant in the GET/O_2 group Exercise efficiency (W/VO_2) at peak exercise on room air increased by 13 (23) W/(L/min) in the GET/RA group ($p< 0.01$), and by 10 (25) W/(L/min) in the GET/O_2 group ($p=0.1$) In both groups the reduction in dyspnoea score was about 1 3 point (p=NS)

The variability between patients in cycling time during *single-stage exercise* was large At the start of the study only three patients were able to cycle at least 10 min, whereas 14 patients stopped within 5 min of exercise Training did not improve cycling time in the GET/RA group In the GET/O_2 group, the increase in cycling time (2 2 (4 2) min) was not significant (p=0 1) (Table 6 3)

Table 6 3 – Single-stage exercise test and activities of daily life breathing room air before and after pulmonary rehabilitation

	GFT/RA		GFT/O_2	
	before	after	before	after
Single-stage cycle exercise test				
Cycling time, *min*	6 5±4 4	6 5±4 4	4 5±2 5	6 7±3 7
Heart rate, *beats/min*	124±22	125±19	116±21	126±21
VE, *L/min*	39±15	40±21	32±14	36±15
VCO_2, *L/min*	1 0±0 4	1 1±0 5	0 8±0 3	1 0±0 4
SaO_2, *%*	86±4	83±6	86±4	83±6
Dyspnoea, *Borg scale*	5 8±0 9	6 2±1 7	6 1±1 8	5 8±1 7
6MWD, *m*	487±191	610±166*	389±140	475±180*
Heart rate, *beats/min*	118±10	126±11	110±23	124±19*
SaO_2, *%*	84±5	82±5	85±6	83±6
Dyspnoea, *Borg scale*	4 8±1 2	5 1±1 6	4 5±1 1	4 8±1 6
Stair climbing, *n*	29±12	41±18*	22±10	30±14*
Weight lifting, *n*	36±14	52±18*	37±9	46±7*

Values are presented as mean ± SD For exercise testing protocols for stair climbing and weight lifting see text SaO_2 arterial oxygen saturation (pulse oximeter), 6MWD 6 min walking distance For further definitions see legends to Tables 6 1 and 6 2
*p<0 01 within-group comparison before versus after rehabilitation

The *6MWD* increased significantly by 123 (77) m in the GET/RA group and by 86 (77) m in the GET/O_2 group This was achieved at a higher heart rate in both groups, which was significant only in the GET/O_2 group (Table 6 3)

The performance during *stair-climbing* and *weight-lifting* increased significantly by 20-40% in both groups (Table 6 3)

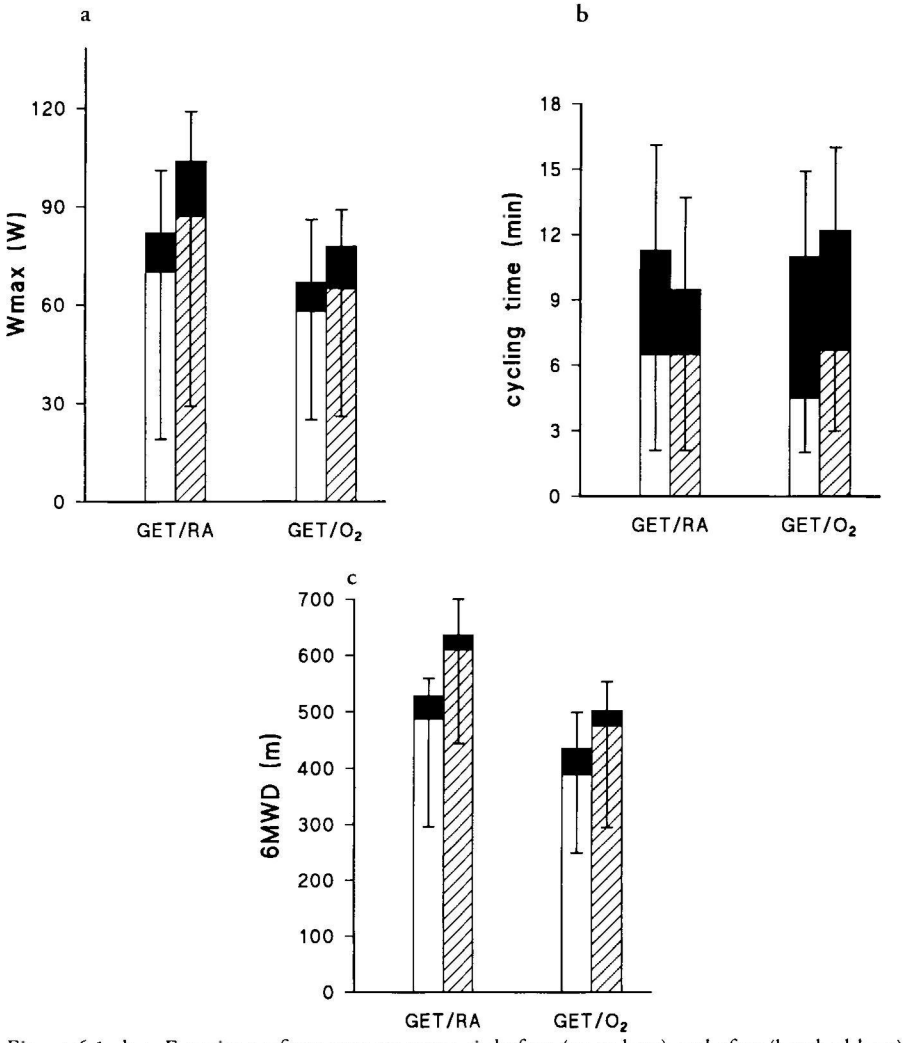

Figure 6.1a,b,c. Exercise performance on room air before (open bars) and after (hatched bars) general exercise training while breathing room air (GET/RA, n=12) and supplemental oxygen (GET/O_2, n=12). The acute effects of supplemental oxygen are depicted in the closed bars. Error bars indicate standard deviation.

6.1a: Training significantly increased maximum work load (Wmax) on room air in the GET/RA group ($p<0.01$), but not in the GET/O_2 group. Supplemental oxygen increased Wmax before and after training in both groups, but these improvements were significant only after training ($p<0.01$). *6.1b:* Training did not improve cycling time during single-stage exercise on room air at a constant work load of 65% of Wmax in both groups. Supplemental oxygen significantly increased cycling time both before and after training in both groups ($p<0.01$). *6.1c:* Training significantly increased 6 min walking distance (6MWD) on room air in both groups ($p<0.01$). Supplemental oxygen significantly increased 6MWD before training in both groups ($p<0.01$). After training, no further improvement in 6MWD was observed. Differences between groups were not significant.

No significant differences were observed in exercise performance, responses to exercise and effects of training between the two groups.

Oxygen-supplemented exercise testing

Supplemental oxygen had acute effects on exercise performance before and after training. The effects did not differ between the two training groups. Before training supplemental oxygen improved Wmax during *maximal incremental cycle exercise* in the GET/RA group by 12 (19) W (p=0.04), and in the GET/O_2 group by 4 (19) W (p=0.15). After training, supplemental oxygen significantly increased Wmax in both groups by 17 (15) and 13 (11) W, respectively (Figure 6.1a).

Supplemental oxygen significantly increased cycling time during *single-stage exercise* before training by 4.8 (4.8) in the GET/RA group and by 6.5 (3.9) min in the GET/O_2 group, and after training by 2.9 (4.3) and 5.5 (3.9) min, respectively (Figure 6.1b).

Before training supplemental oxygen significantly increased *6MWD* by 42 (30) in the GET/RA group and by 47 (63) m in the GET/O_2 group (Figure 6.1c). The acute effect of oxygen on 6MWD was lost after training.

Table 6.4 Oxygen supplemented exercise testing before and after pulmonary rehabilitation

	GET/RA		GET/O_2	
	before	after	before	after
Maximal incremental cycle exercise test	82±53	104±68*#	62±27	79±40*#
Wmax, *W*	132±21	139±30	123±19	129±21
Heart rate, *beats/min*	41±20	45±23	35±14	39±17
$\dot{V}E$, *L/min*	1.2±0.6	1.4±0.7*#	1.0±0.4	1.2±0.5*#
$\dot{V}CO_2$, *L/min*	94±3	94±4	93±5	93±6
SaO_2, *%*	5.8±1.5	6.3±1.4	6.4±2.3	5.8±1.9
Dyspnoea, *Borg scale*				
Single-stage cycle exercise test				
Cycling time, *min*	11.4±4.7#	9.4±5.2#	11.0±4.5#	12.2±4.4#
Heart rate, *beats/min*	129±18	125±20	121±18	127±25
$\dot{V}E$, *L/min*	38±15	39±21	34±15	36±14
$\dot{V}CO_2$, *L/min*	1.1±0.4	1.1±0.5	0.9±0.3	1.0±0.3
SaO_2, *%*	95±2	95±2	95±2	95±2
Dyspnoea, *Borg scale*	6.0±1.5	5.7±2.2	6.3±2.1	5.0±1.5
6MWD, *m*	529±193#	637±221*	436±162#	504±164*
Heart rate, *beats/min*	121±11	125±15	111±24	121±22*
SaO_2, *%*	90±5	87±8	92±3	91±3
Dyspnoea, *Borg scale*	4.8±1.5	4.7±1.5	4.8±2.6	4.3±1.4

Table 6.4. Values are presented as mean ± SD. For definitions see legends to Tables 6.1-6.3.
*p<0.01: within-group comparison before versus after rehabilitation.
#p<0.01: oxygen-supplemented exercise test versus exercise test on room air.

The acute effects of oxygen on Wmax, cycling time and 6MWD before training did not differ significantly from those after training.

Training significantly increased Wmax, peak VCO_2 and 6MWD while breathing oxygen, to a similar extent in both groups (Table 6 4). The increase in 6MWD was achieved at a higher heart rate in the GET/O_2 group, while the heart rate did not change in the GET/RA group. Differences between groups were not significant.

Quality of life

Before rehabilitation CRDQ scores were similar in both groups. Rehabilitation significantly increased total CRDQ score by 15 (7) points in the GET/RA group and by 19 (14) points in the GET/O_2 group. The improvements were equally distributed among the four dimensions, but were not significant for the dimension fatigue in both groups and for emotional function in the GET/RA group (Table 6.5).

Table 6 5 Quality of life (CRDQ) before and after pulmonary rehabilitation

	GET/RA		GET/O_2	
	before	after	before	after
Dyspnoea	14 9±5 8	21 6±4 5*	15 9±5 3	21.6±5 5*
Fatigue	17 4±4 8	20 0±4 5	15 5±4 3	18 8±3 9
Emotional function	32 0±6 9	35 2±8 5	29 5±7 1	35 3±6 3*
Mastery	20 4±4 1	22 8±3 7*	18 0±5 5	22 1±3 3*
Total score	85±16	100±17*	79±18	98±16*

Values are presented as mean ± SD CRDQ Chronic Respiratory Disease Questionnaire For further definitions see legend to Table 6 1

*p<0 01 within-group comparison before versus after rehabilitation

6.5 Discussion

In this study, we investigated whether patients with severe COPD and hypoxaemia at peak exercise might benefit from supplemental oxygen during training. Exercise training, both on air and oxygen, improved exercise performance and quality of life. Although supplemental oxygen had acute beneficial effects on exercise performance, oxygen-supplemented exercise training did not add to the effects of training while breathing room air.

The diffusion capacity below 50% of predicted[30], the elevated P(A-a)O_2 at rest and the increase in P(A-a)O_2 by more than 3 kPa during exercise[31] indicate that a diffusion-perfusion limitation, rather than hypoventilation was the cause of the hypoxaemia at peak exercise in these patients.[1,32]

Pulmonary rehabilitation in patients with severe COPD

Several studies have reported beneficial effects of pulmonary rehabilitation in patients with moderate-to-severe COPD, some of whom were hypoxaemic at rest or during exercise.[13-15,33,34] These studies showed improvements in maximal work load[14,15], endurance exercise capacity[13-15,34], walking distance[13], perceived breathlessness[14,15] and quality of life[13]. A physiologic training effect in terms of an increase in peak $\dot{V}O_2$, and reduction in heart rate, blood lactate levels and ventilation at identical work rates after training, has been reported in some studies[14,15,34], but was not found by others.[13,33] The effects in patients who developed hypoxaemia during the training were not described separately.

The patients in the present study were normoxic at rest and hypoxaemic at peak exercise. During the training they desaturated, but SaO_2 was not allowed to fall below 90%. Training did not increase aerobic capacity while breathing room air. The improvement in exercise performance was achieved in part by an improvement in exercise efficiency ($W/\dot{V}O_2$). Since the Borg score at peak exercise tended to decrease after training, both desensitization to dyspnoea and motivation may have played a role in patients in whom training proportionally improved Wmax and peak $\dot{V}O_2$.

Acute effects of supplemental oxygen on exercise performance

In patients with COPD, the acute administration of supplemental oxygen has been shown to improve exercise performance.[3-6] Breathing supplemental oxygen increased Wmax during cycle exercise by 10%[6], endurance cycling and walking time by 88% and 59%, respectively, and 6MWD by 17%[5] in comparison with room air. We found similar results in the present patients. Since the ventilatory equivalent for oxygen is higher for walking than for cycling, and 6MWD is a submaximal exercise test, diffusion-perfusion may be less important as a factor limiting 6MWD. Hence, the acute effect of supplemental oxygen on 6MWD was small as compared to performance during cycling at high exercise intensities. After training, this difference became even more clear, as breathing oxygen did not improve 6MWD further in comparison with room air. This was caused, in part, by the effect of training on 6MWD, which far exceeded the acute effect of oxygen.

Effects of oxygen-supplemented exercise training

Few studies have investigated the effects of training with supplemental oxygen in patients with COPD. In the study by Zack and Palange[17], oxygen-supplemented training significantly increased Wmax while breathing oxygen, whereas Wmax and peak $\dot{V}O_2$ on room air did not improve. Endurance cycling time and 12 min walking distance significantly improved both on air and oxygen.[17] Degre et al.[16] reported an increase in peak $\dot{V}O_2$ by 10% after training with supplemental oxygen (3-4 L/min), which was related to the PO_2 during exercise.[16] Maximal cardiac

output and stroke volume did not change [16] In these studies, however, no comparison was made with a control group breathing room air

In the present study, training with supplemental oxygen did not add to the effects of training on room air Recently, similar results have been reported in patients who did not desaturate during exercise [35] Comparing exercise tests on oxygen, however, our study showed that training improved Wmax and peak VCO_2 (VO_2 could not be measured under these conditions) in both groups This implies a physiologic training effect, regardless of the use of oxygen during the training These training effects were not observed during exercise testing on room air, possibly because hypoxaemia limited exercise performance

In contrast to previous studies, training with or without supplemental oxygen did not improve endurance cycling time on air and oxygen in present patients [13 15 17 34] Furthermore, endurance work (constant work load x endurance cycling time) did not improve in either group Study population and test design may explain the results in our study Hypoxaemia and the high constant work load, which was adjusted to the actual Wmax after training, may have contributed to the poor performance during the single-stage exercise test on room air Indeed, endurance cycling time increased considerably when oxygen was administered However, the single-stage test was limited to 15 min, which may have concealed some of the effects of training

Many factors may account for the absence of an additional effect of training with supplemental oxygen, as observed in the present study Firstly, the contribution of hypoxaemia to the exercise limitation is still uncertain and the mechanisms by which oxygen affects exercise performance are complex [6 11] The present study confirmed previous reports showing that the acute effects of oxygen, as well as the effects of training, correlated poorly with lung function parameters or blood gases at rest or during exercise [5 6 17] Furthermore, in the present study, the acute effects of oxygen did not predict the effects of training in individual subjects Hence, patients with a poor response to oxygen are not necessarily poor candidates for training These findings suggest that oxygen and training may influence exercise performance by different mechanisms

Secondly, in spite of the acute effects of oxygen, the GET/O_2 group did not achieve higher work rates during cycle exercise training than the GET/RA group Thus, the total amount of work performed during the training was equal in both groups This was due to the training regimen, which consisted of interval training with bouts of exercise of 3 min or less Endurance exercise was not performed during the training Thus, the GET/RA group could keep SaO_2 above 90% at relatively high work rates As a result, during exercise training, the patients in both groups were similarly limited by their ventilatory impairment and by breathlessness rather than by hypoxaemia

Thirdly, increased blood lactate levels during exercise have been shown to enhance the effects of training in patients with COPD [34] In healthy subjects and

in patients with peripheral vascular disease, muscle ischaemia is a potent stimulus for improving endurance exercise.[36] Since supplemental oxygen abolishes the desaturation and reduces lactate levels during exercise[4,37], it might also have reduced the training stimulus in the present patients.

Finally, in addition to the diffusion-perfusion limitation in the lungs, a diffusion limitation at the level of the skeletal muscles may be present.[38,39] In healthy subjects under hypoxaemic conditions, muscle diffusion capacity was an important factor limiting maximal $\dot{V}O_2$, especially in deconditioned muscles.[39] Supplemental oxygen may, thus, fail to enhance muscle oxygen utilization during the training in patients with COPD in whom peripheral muscle weakness may exist.[40]

Clinical implications and conclusions

Supplemental oxygen attenuates the increase in MPAP during exercise in patients with COPD.[41] However, it is unknown whether this may prevent the development of pulmonary hypertension. In the present study training did not change resting MPAP. Thus, training both on air and oxygen may be safe, as long as SaO_2 is kept above 90% during exercise.

This study shows that pulmonary rehabilitation improves functional capacity and quality of life in patients with severe COPD and hypoxaemia at peak exercise. The increase in quality of life scores after pulmonary rehabilitation is considered clinically relevant[42], and is in agreement with previous studies.[43] Breathing supplemental oxygen during the training had no advantage over training while breathing room air.

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CHAPTER 7

Additional eccentric exercise training in patients with COPD and hypoxaemia at peak exercise

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Submitted

7.1 Abstract

Study objective – The metabolic cost and ventilatory requirements of eccentric exercise are lower than those of concentric exercise at similar work loads. The aim of this study was to investigate the effects of additional eccentric exercise training in patients with chronic obstructive pulmonary disease (COPD) and exercise-induced hypoxaemia

Patients and methods – In a randomized trial, we studied the effects of eccentric exercise training (EET) in addition to general exercise training (GET) on exercise performance and quality of life in 24 patients with severe COPD and a normal resting PaO_2, who developed hypoxaemia during maximal incremental cycle exercise (SaO_2 < 90% at peak exercise). The patients participated in a comprehensive in-patient pulmonary rehabilitation programme of 10 weeks. They were randomly assigned either to GET (GET group: mean FEV_1 38% predicted; PaO_2 7.3 kPa at maximum exercise) or GET with additional EET (GET/EET group: FEV_1 45% predicted; PaO_2 7 7 kPa at maximum exercise)

Results – GET and GET/EET both improved maximum work load (Wmax) during maximal incremental cycle exercise, 6 min walking distance, activities of daily life (stair-climbing and weight-lifting) and quality of life. Beneficial changes in the physiologic response to exercise were observed in the GET/EET group. Heart rate at rest and at Wmax was lower after training in the GET/EET group, whereas heart rates did not change in the GET group. The increase in $P(A\text{-}a)O_2$ during maximal cycle exercise was also less in the GET/EET group, but remained unchanged in the GET group The creatinine height index increased by 8% in both groups, but this was significant only in the GET/EET group. Differences between both groups were not significant

Conclusions – Pulmonary rehabilitation improved exercise performance and quality of life similarly in both training groups of patients with COPD and hypoxaemia at peak exercise. Physiologic training effects were observed only in the group which had trained eccentrically

7.2 Introduction

The exercise capacity in patients with chronic obstructive pulmonary disease (COPD) is reduced. This may be due to impaired pulmonary mechanics, ventilatory muscle function, gas-exchange and pulmonary haemodynamics.[1] Exercise-induced hypoxaemia may be a factor that further reduces mobility. The reduction in daily life activities will lead to peripheral muscle deconditioning.[2]

Pulmonary rehabilitation has been shown to improve exercise performance in patients with COPD. In general, these patients had moderate to severe airway obstruction, but most of them were not hypoxaemic during exercise. Exercise training resulted in a physiologic training effect in terms of an increase in peak VO_2[3 6] and a reduction in lactate and ventilation at equivalent work loads[6 7] or improved muscular efficiency and coordination[8 10] and symptoms of perceived breathlessness[4 6]. Inspiratory muscle training may improve respiratory muscle strength and endurance [11] Specific training of isolated peripheral muscles may provide an additional training stimulus, since it can be performed at a higher intensity than whole body exercise [12]

Dynamic exercise can be accomplished either by concentric (positive work) or eccentric muscle contractions (negative work). During eccentric exercise (e.g. lowering a weight) the contracting muscle lengthens in a controlled way, whereas during concentric exercise (e g. lifting a weight) the muscle shortens.[13] At similar work loads, fewer motor units are activated during eccentric than during concentric exercise.[14] This is associated with a reduced oxygen cost and ventilatory requirement In healthy subjects, VE and VO_2 were 30-50% lower during eccentric than during concentric exercise at similar work loads.[13 15 17]

If these reductions in ventilatory requirements would also occur in patients with severe COPD, e.g. those who develop hypoxaemia during concentric exercise, these patients may also benefit from eccentric exercise training during pulmonary rehabilitation. Indeed, we found a reduction of 30% in VE and VO_2 during eccentric cycle exercise testing in comparison with concentric exercise at given constant work loads up to 50% of maximum in patients with COPD [18] We hypothesized that eccentric exercise enables these patients to train at a higher intensity and for a longer duration, and may thus offer an additional training stimulus. Therefore, we compared the effects of general exercise training with the effects of additional eccentric exercise training on exercise performance and quality of life in patients with COPD and hypoxaemia at peak exercise. Furthermore, we studied the physiologic response to both training modalities.

7.3 Methods

A randomized study was undertaken in 24 patients with stable COPD according to the American Thoracic Society (ATS) criteria[19]. All were referred to our hospital for pulmonary rehabilitation. They met the following inclusion criteria: hypoxaemia (arterial oxygen saturation (SaO_2) < 90%) at maximum exercise, and an increase in alveolar-arterial difference in oxygen tension ($P(A\text{-}a)O_2$) of at least 2 kPa from rest to maximum exercise during maximal incremental cycle exercise. Patients were excluded if they had a resting PaO_2 of less than 8.5 kPa, a mean nocturnal SaO_2 of less than 90%, a mean pulmonary artery pressure (MPAP) of more than 25 mmHg measured at rest by Doppler echocardiography[20], and if they had neuromuscular or cardiovascular disease.

All patients were ex-smokers. Their medication was not changed during the study. They were familiar with the procedures of exercise testing. The patients were randomly allocated to a group receiving general exercise training (GET), or to a group receiving GET with additional eccentric exercise training (GET/EET). Informed consent was obtained from each patient. The study was approved by the hospital ethics committee.

Pulmonary rehabilitation programme

All patients participated in a multidisciplinary in-patient programme for 10 weeks, which consisted of physical training, breathing retraining, physical therapy (relaxation and mobilization exercises), education and psycho-social support.

General exercise training (GET)

Training consisted of dynamic and isometric strength training and specific training of daily life activities. Training sessions were held 5 days per week and had a mean duration of 80 min, including periods of rest. GET comprised the following exercises: interval cycling (2 min of exercise alternated with 2 min of rest for 20 min), rowing (5 min), dynamic exercises for the muscles of the arm and shoulder-girdle using a pulley (5 min), and for the muscles of the back and abdomen by lifting the upper body and the legs, respectively, from the supine position (5 min), isometric strength training of the arms, shoulder-girdles and legs (3 min), Stair-climbing (3 min), sitting down and getting up from a chair alternated with slalom walking (5 min), arm exercise by moving a weight of 1-2 kg between racks at 20 cm above and below shoulder level (5 min). All sessions were supervised by a physiotherapist. SaO_2 during exercise was monitored with a pulse oximeter using a finger probe (Oxyshuttle, Sensor Medics, Bilthoven, The Netherlands). Exercise training was started at low work loads. After the first week, the exercise intensity was gradually increased as tolerated by the patients. In both groups, the work rate during the various exercises was not allowed to exceed the level at which SaO_2 fell below 90%.

Eccentric exercise training (EET)
The GET/EET group performed eccentric exercise after each training session on an electrically-braked cycle ergometer (Lode, Groningen The Netherlands), which was adapted for negative work [21] The pedals were driven in backward direction by an electric motor at a rate of 60 revolutions per minute (RPM). The electromagnetic brake of the ergometer was set at the desired work load for the subject. The motor had to generate the same power to overcome this resistance. During this procedure the subjects were asked to let their legs be moved passively. Subsequently, the electric brake was withdrawn and the subjects were instructed to brake the speed of the pedals, and to maintain a pedalling rate of 60 RPM. From that moment, the power generated by the motor to overcome the resistance of the electric brake was absorbed by the patient, who then performed negative work at an equivalent load Since eccentric exercise is associated with delayed muscle soreness and muscle damage[22], training was started with 5 min of exercise at a work rate of 30% of Wmax during concentric cycling During the first two weeks, negative work was extended with small increments in exercise duration Afterwards, the exercise intensity was adjusted to the highest work rate, which could be sustained for 15 min.

Outcome measures
Pulmonary function tests
Spirometry and the transfer coefficient for carbon monoxide (KCO, single breath) were performed according to European Respiratory Society (ERS) standards.[23] Maximal inspiratory esophageal pressure ($PI_{oes\,max}$) in sitting position was measured with a pressure transducer (Validyne, Northridge, California) during sniff manoeuvres from residual volume [24] All tests, as well as Doppler echocardiography at rest, were repeated at the end of the training period.

Nutritional state
Body weight was measured and body mass index was calculated (kg/m^2). Skeletal muscle mass was assessed by measurement of the creatinine height index, which was calculated by dividing 24 h urinary creatinine excretion by a reference value based on ideal body weight.[25]

Maximal incremental cycle exercise test
The patients cycled concentrically on an electrically-braked cycle ergometer (Lode, Groningen, The Netherlands) at a pedalling rate of 60 RPM, breathing room air. The work rate was increased each minute by 10% of the estimated maximal work load (Wmax), until exhaustion [26] Arterial blood samples were drawn from an indwelling catheter in the brachial artery. Minute ventilation (VE), oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured every 30 s by a mixing chamber ergospirometry unit (Oxycon IV, Mijnhardt, Maarsen,

The Netherlands) Breathlessness was scored on a modified Borg scale [27] Peak VE was related to predicted maximal exercise values (VEmax predicted = 37 5 x FEV_1) [28]

Single-stage cycle exercise test
After 1 min of unloaded pedalling, exercise was performed at a constant work load of 65% of the actual Wmax Endurance cycling time was measured The test was terminated when the patient could not sustain exercise any longer, or after a maximum of 15 min The same measurements were made as during the maximal incremental test, except for bloodgas analysis

Activities of daily life
After 3 practise tests, the 6 min walking distance (6MWD) was measured in a gymnasium [29] SaO_2 was measured continuously and dyspnoea was scored at the end of the test

Stair-climbing was performed on an exercise staircase with a hand-rail, which had 4 steps for going up, a plateau, and 3 steps for going down The number of rounds during 5 min of exercise were counted Similar measurements were made as during 6MWD

During weight-lifting the patients held a weight of 2 kg in the predominant hand and moved it between racks at 20 cm above and below shoulder level The number of lifts to both levels during 3 min was counted [30]

Quality of life
Quality of life was assessed by means of the Chronic Respiratory Disease Questionnaire (CRDQ) [31] This questionnaire examines the dimensions dyspnoea, fatigue, emotional function and mastery Altogether 20 items are scored on a seven-point scale (maximum score 140 points, a higher score indicates a better quality of life) The test was administered at the start of the study and 6 weeks after completion of the pulmonary rehabilitation programme

Statistical analysis
The data were analysed with the Statistical Analysis System (SAS) package (SAS Institute Inc , Cary, NC, USA) The results were expressed as mean ± SD Changes within the training groups were compared with the Wilcoxon test for paired samples Differences between the groups were compared with the Kruskal Wallis test (Chi-square approximation) Significance was accepted at a p-value of less than 0 05

7.4 Results

Measurements at rest

The patients had severe airway obstruction, a reduced transfer coefficient for carbon monoxide and an elevated resting $P(A\text{-}a)O_2$, but they were normoxic at rest (Table 7.1). Between groups no significant differences were observed. After pulmonary rehabilitation no changes were observed in lung function parameters, $PI_{oes\ max}$, MPAP and gas exchange at rest. Resting heart rate was lower after training in the GET/EET group (78 versus 88 beats/min). The creatinine height index increased by 8% in both groups, but this was significant only in the GET/EET group ($p<0.05$).

Table 7.1 Patient characteristics and pulmonary function at rest before and after pulmonary rehabilitation

	GET		GET/EET	
	before	after	before	after
Patients, *n*	12		12	
Sex, *M/F*	10/2		10/2	
Age, *yrs*	59±13		59±10	
BMI, *kg/m²*	23.2±1.6	23.0±1.6	24.7±4.1	24.8±3.6
Creatinine Height Index, *%*	86±27	94±28	82±33	90±35*
TLC %predicted, *%*	114±20	110±11	115±23	114±25
IVC %predicted, *%*	93±19	95±17	97±18	99±21
FEV_1, *L*	1.2±0.5	1.2±0.5	1.4±0.4	1.4±0.4
FEV_1 %predicted, *%*	38±11	38±12	45±13	44±10
KCO %predicted, *%*	37±14	40±15	41±17	40±16
$PI_{oes\ max}$, *kPa*	8.0±2.7	8 6±2.9	6.7±2.0	7.0±1 4
Heart rate, *beats/min*	92±19	87±15	88±15	78±16*
MPAP, *mmHg*	13±3	16±7	15±4	16±5
PaO_2, *kPa*	10 5±1.1	10.2±1.3	10.4±1.3	10.6±1.3
$PaCO_2$, *kPa*	5.0±0.8	4.9±0.6	5.0±0.6	4.9±0.5
$P(A\text{-}a)O_2$, *kPa*	4.4±0.9	5 2±1.6	4.4±1.4	4.9±1.4

Values are presented as mean ± SD. GET: general exercise training; GET/EET: general exercise training/eccentric exercise training; BMI: body mass index; TLC: total lung capacity (He-dilution); IVC: inspiratory vital capacity; FEV_1: forced expiratory volume in one second; KCO: transfer coefficient for carbon monoxide (single-breath); $PI_{oes\ max}$: maximal inspiratory oesophageal pressure; MPAP: mean pulmonary artery pressure; PaO_2: arterial oxygen tension; $PaCO_2$: arterial carbon dioxide tension; $P(A\text{-}a)O_2$: alveolar-arterial difference in oxygen tension.
*p<0 01: within-group comparison before versus after rehabilitation.
No significant differences were present between groups.

Cycle exercise intensity during the training

During the last six weeks of the training period the mean work load achieved during interval cycle exercise training in the GET group and in the GET/EET group was 114 (32) and 106 (23) % of Wmax, respectively During EET the patients were able to cycle continuously for 15 min at an intensity of 160 (69) % of Wmax achieved during concentric exercise

Maximal incremental cycle exercise test

Before training the response to maximal incremental cycle exercise was similar in both groups (Table 7 2). VE at peak exercise approximated predicted maximal exercise values. $PaCO_2$ increased by 0 7 kPa in the GET group and by 0.4 kPa in the GET/EET group. PaO_2 decreased by about 3 kPa and the increase in $P(A\text{-}a)O_2$ ($\Delta P(A\text{-}a)O_2$) was more than 3 kPa in both groups

Table 7 2 Maximal incremental and single-stage cycle exercise testing before and after pulmonary rehabilitation

	GET		GET/EET	
	before	after	before	after
Maximal incremental cycle exercise test				
Wmax, *W*	70±51	87±58**	75±40	85±47*
Heart rate, *beats/min*	133±21	132±23	124±13	120±10*
VE, *L/min*	43±21	43±21	46±11	46±12
VE %VEmax pred , %	96±23	95±18	90±19	89±14
VO_2, *L/min*	1 2±0 5	1 2±0 6	1 3±0 4	1 3±0 4
O_2 pulse, *mL O_2/beat*	8 7±2 3	9 3±3 2	10 4±2 8	11 4±2 5
PaO_2, *kPa*	7 3±0 7	6 9±0 7*	7 7±0 5	7 9±0 9#
$PaCO_2$, *kPa*	5 7±1 1	5 7±0 8	5 4±0 9	5 5±0 9
Δbase excess, *mmol/L*	-5 3±2 8	-5 7±2 8	-6 2±2 7	-5 4±2 5
$P(A\text{-}a)O_2$, *kPa*	7 7±1 3	8 2±1 5	7 9±1 1	7 4±1 4
$\Delta P(A\text{-}a)O_2$, *kPa*	3 3±0 9	3 0±1 8	3 5±1 1	2 5±1 6*
Dyspnoea, *Borg scale*	7 3±2 4	5 8±1 9	7 3±2 4	5 8±2 2
Single-stage cycle exercise test				
Cycling time, *min*	6 5±4 4	6 5±4 4	6 2±3 4	6 4±2 2
Heart rate, *beats/min*	124±22	125±19	122±17	122±12
SaO_2, %	86±4	83±6	88±4	87±3
Dyspnoea, *Borg scale*	5 8±0 9	6 2±1 7	6 1±2 0	5 2±2 0

Values are presented as mean ± SD Wmax maximum work load, VE minute ventilation, VO_2 oxygen consumption, VCO_2 carbon dioxide production, Δbase excess change in base excess, $\Delta P(A\text{-}a)O_2$ change in $P(A\text{-}a)O_2$, SaO_2 arterial oxygen saturation (pulse oximeter) For further definitions see legend to Table 7 1

*p<0 05, ** p<0 01 within-group comparison before versus after rehabilitation

#p<0 05 comparison between GET and GET/EET

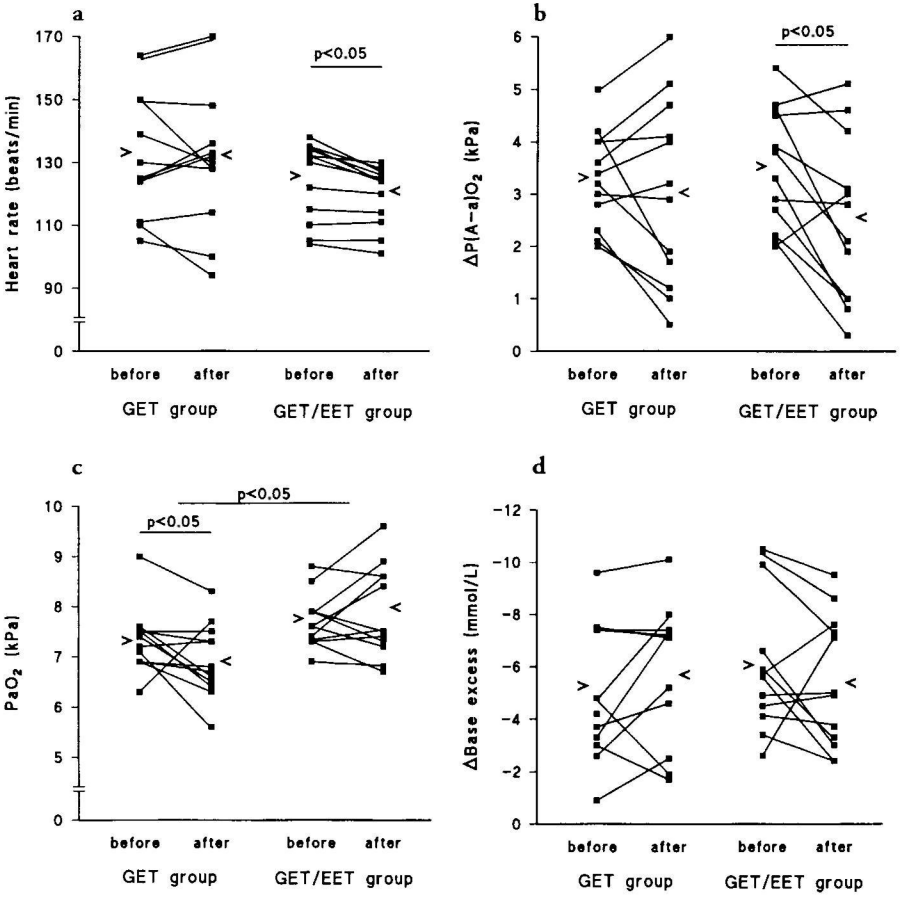

Figure 7.1a,b,c,d. Maximum heart rate (7.1a), change in P(A-a)O_2 (ΔP(A-a)O_2; 7.1b), PaO_2 (7.1c) and change in base excess (Δbase excess; 7.1d) achieved during a maximal incremental cycle exercise test before and after training for each subject in the general exercise training group (GET group) and in the general exercise training/eccentric exercise training group (GET/EET group). The markers indicate mean values.

Wmax increased at the end of the training programme in the GET group by 17 (15) W ($p<0.01$) and in the GET/EET group by 10 (12) W ($p<0.05$). Peak $\dot{V}E$, $\dot{V}O_2$ and oxygen pulse did not change in either group. The score for dyspnoea at Wmax was reduced by about 1.5 point in both groups, but these changes did not reach statistical significance. No differences between the GET and the GET/EET group were observed in these indices.

After GET/EET, heart rate at Wmax was lower than the heart rate reached at Wmax before training (120 versus 124 beats/min, $p<0.05$). No change was observed in the GET group (132 versus 133 beats/min, p=NS) (Figure 7.1a). The ΔP(A-a)O_2 at Wmax was also lower after GET/EET (2.5 versus 3.5 kPa, $p<0.05$),

whereas these values did not change in the GET group (3 0 versus 3 3 kPa, p=NS) (Figure 7 1b) These responses to maximal exercise were not statistically different between the two groups PaO_2 at maximum exercise showed a further decrease after training in the GET group (6 9 versus 7 3 kPa, p<0 05), but remained unchanged in the GET/EET group (7 9 versus 7 7 kPa, p=NS) (GFT versus GET/EET p<0 05) (Figure 7 1c) After GET/EET the base excess at Wmax was reduced less (5 4 versus -6 2 mmol/L), whereas a further decrease was observed after GET (-5 7 versus -5 3 mmol/L) However, these changes were not significant within or between groups (Figure 7 1d)

Single-stage cycle exercise test

The variability in cycling time between patients was large At the start of the study only three patients were able to cycle the full 15 min, whereas 10 patients stopped within 5 min of exercise Training did not improve endurance cycling time in either group (Table 7 2)

Activities of daily life

6MWD increased in the GET group and in the GET/EET group by 123 (77) and 118 (66) m (both groups p<0 01), respectively (Table 7 3) In the GET group the improvement in 6MWD was achieved at a higher heart rate in comparison with the heart rate during 6MWD at baseline (126 versus 118 beats/min, p<0 05) Such increase in heart rate was not observed in the GET/EET group (117 versus 113 beats/min, p=NS) SaO_2 at the end of the test showed a further decrease after training than at baseline in both groups, but this was significant only in the GET group (SaO_2 82 versus 84%, p<0 05) Dyspnoea scores remained unchanged Between the two groups no significant differences in these responses were found

The performance during stair-climbing and weight-lifting improved by 20-40% in both groups (Table 7 3) Heart rate, SaO_2 and dyspnoea scores during stair-climbing did not change significantly in both groups Differences in responses between the two groups were not present

Quality of life

At the start of the study the dimension mastery (6 points) and the total CRDQ score (17 points) were significantly lower in the GET/EET than in the GET group (p<0 05) (Table 7 4)

After pulmonary rehabilitation the total CRDQ score increased significantly by 15 (7) points in the GET group and by 16 (11) points in the GET/EET group (p<0 01) No differences in response between the two groups were observed

Table 7 3 – Activities of daily life before and after pulmonary rehabilitation

	GET		GET/EET	
	before	after	before	after
6MWD, *m*	487±191	610±166**	445±142	563±128**
Heart rate, *beats/min*	118±10	126±11*	113±16	117±14
SaO_2, *%*	84±5	82±5*	88±5	85±6
Dyspnoea, *Borg scale*	4 8±1 2	5 1±1 6	4 6±0 7	4 9±1 6
Stair-climbing, *n*	29±12	41±18**	27±11	38±13**
Heart rate, *beats/min*	126±11	132±20	123±15	123±18
SaO_2, *%*	85±7	81±7	85±5	85±6
Dyspnoea, *Borg scale*	5 7±1 3	5 6±1 6	5 4±1 6	5 4±2 1
Weight-lifting, *n*	36±14	52±18**	33±9	40±9*

Values are presented as mean ± SD 6MWD 6 min walking distance For exercise testing protocols for stair-climbing and weight-lifting see text For further definitions see legends to Tables 7 1-7 2
*p<0 05, ** p<0 01 within-group comparison before versus after rehabilitation
No significant differences were present between groups

Table 7 4 – Quality of life (CRDQ) before and after pulmonary rehabilitation

	GET		GET/EET	
	before	after	before	after
Dyspnoea	14 9±5 8	21 6±4 5**	14 6±5 9	18 8±4 5**
Fatigue	17 4±4 8	20 0±4 5*	12 9±4 4	16 9±4 6*
Emotional function	32 0±6 9	35 2±8 5*	25 9±11	30 0±8 9*
Mastery	20 4±4 1	22 8±3 7**	14 4±5 9#	18 6±4 8**
Total score	85±16	100±17**	68±23#	84±18**

Table 7 4 Values are presented as mean ± SD CRDQ chronic respiratory disease questionnaire For further definitions see legend to Table 7 1
*p<0 05, ** p<0 01 within-group comparison before versus after rehabilitation
#p<0 05 comparison between GET and GET/EET

7.5 Discussion

The present study demonstrates that pulmonary rehabilitation is feasible in patients with severe COPD who develop hypoxaemia during exhausting exercise. Pulmonary rehabilitation had positive effects on maximum work load, activities of daily life and measures of quality of life Addition of EET to GET did not result in a further improvement. Only within the GET/EET group the improvements in

exercise performance were accompanied by significant reductions in heart rate and in $\Delta P(A\text{-}a)O_2$ at Wmax, and by an increase in the creatinine height index However, no significant differences in these parameters were observed after training between the GET and the GET/EET group

This study was undertaken in patients with COPD and hypoxaemia at peak exercise Exercise-induced hypoxaemia may arise from hypoventilation, or from a limitation in oxygen-uptake and transport capacity due to a diffusion limitation, shunt, ventilation to perfusion inequality, or a low mixed venous PO_2 (low cardiac output) The diffusion capacity below 50% of predicted[32], the elevated $P(A\text{-}a)O_2$ at rest and the increase in $P(A\text{-}a)O_2$ by more than 3 kPa during exercise[33] indicate that a diffusion-perfusion limitation rather than hypoventilation was the cause of the hypoxaemia during exercise in the present patients [1 34]

In patients with COPD, hypoxaemia contributes to the increase in the pulmonary artery pressure during exercise, the long-term effects of which are unknown [35] In both groups, SaO_2 during the training was kept above 90%, and MPAP at rest remained unchanged after training Thus we assume that exercise training can be safely performed in this selected group of patients with COPD We have no good explanation why in the GET group PaO_2 at Wmax was significantly lower after training, since lung function, peak VO_2 and VE as well as $PaCO_2$ and $P(A\text{-}a)O_2$ both at rest and exercise did not change

Many studies in patients with moderate and severe COPD have shown beneficial effects of pulmonary rehabilitation on maximum work load[3 6], endurance exercise capacity[4 5 7 31], walking distance[3 36 37], symptoms of perceived breathlessness[4 6] and quality of life[36 38] In these studies, exercise training appeared to improve endurance exercise capacity more than maximal exercise performance [4 5 7 36] In our study, endurance cycling time varied widely between subjects and did not increase significantly after training in both groups This was possibly due to patient selection and to the high constant work load, which was adjusted to the actual Wmax after training Endurance work (constant work load times endurance cycling time) did not improve as well However, the gains in 6MWD and other specific daily life activities were considerable in both groups, as compared to the study of Wijkstra et al , who found only a very small increase in 6MWD (9 m) after 12 weeks of rehabilitation at home [6] The in-patient pulmonary rehabilitation programme (10 weeks) and the frequency of the training sessions (5 days per week) may have contributed to the favourable results in our study The increase in CRDQ by 15 points in our study is regarded to be clinically relevant[39] and is in agreement with previous studies in patients with COPD [37 38]

A physiologic training effect of exercise training is more difficult to achieve, as it may depend on the severity of the disease, the physical fitness and the training intensity Casaburi et al [7] showed reductions in ventilation and blood lactate levels at similar work rates after training in patients with moderate airway obstruction (FEV_1 56% of predicted) Training at a high work rate was more effective than

training at a low work rate Only high work rate training reduced the heart rate during exercise at similar work loads [7] In patients with more severe airway obstruction, training has also been shown to improve aerobic capacity [3 6] This was not confirmed by others who did not find increases in peak VO_2 or decreases in heart rate relative to oxygen consumption after training [8 10] In the study of Belman and Kendregan, training also did not increase enzyme concentrations in the peripheral muscles [10] In our study, GET did not result in a physiologic training effect as well Thus, improvements in exercise performance may have been achieved by an improvement in muscular efficiency and coordination, and desensitization to dyspnoea

Looking for training modalities which may additionally improve exercise capacity in these severely disabled COPD patients, this is the first study investigating the effects of eccentric exercise training Both muscular tension and metabolic cost are stimuli which increase muscle strength [40 41] For the same metabolic cost higher forces are generated during eccentric than during concentric muscle contractions [13] In a recent animal study, more sarcomeres were produced during eccentric than during concentric treadmill exercise [42] In normal subjects, concentric and eccentric muscle training similarly improved static and concentric dynamic strength by 10-30%, and cross-sectional area of the trained muscles by 5%[41 43] If both types of training were combined the gain in muscle strength was greater than during concentric muscle training only [44] The low ventilatory requirement and increased muscular tension during eccentric muscle contractions may make this type of exercise suitable for training patients with limited cardiorespiratory reserves

Indeed, in the present patients the amount of work performed during EET was greater than during GET During EET the patients were able to cycle continuously for 15 min at an intensity of 160% of Wmax without being distressed by dyspnoea In comparison, the work load achieved during 10 min of intermittent concentric cycling was 110% of Wmax in both training groups Exercise-induced muscle damage was prevented by using low exercise intensities, especially during the first two weeks [45] All patients experienced some muscle soreness, but this was well tolerated

Nevertheless, GET/EET did not additionally improve exercise performance in comparison with GET Beneficial changes in heart rate and gas exchange during maximal and submaximal exercise after training, however, were found in the GET/EET group, which may indicate a physiologic training effect In contrast, the improvements in exercise performance in the GET group were achieved at similar or increased heart rates, but differences between groups were not significant Since heart rate at rest and exercise was lower after training in the GET/EET group, but diffusion capacity and blood gases at rest and exercise did not worsen, the reduced $\Delta P(A\text{-}a)O_2$ at maximum exercise is explained by an increase in mixed venous PO_2 resulting from an increase in stroke volume and cardiac output Although not significant, O_2 pulse tended to be increased at Wmax after training In the study by Degre et al [8], training did not improve maximal cardiac output

and stroke volume. Patients in whom peak VO_2 increased, showed a concomitant increase in $P(A\text{-}a)O_2$.[8] In the present study, a significant increase in creatinine height index, reflecting peripheral muscle mass, was observed in the GET/EET group. Again, no differences were found between both training groups Although the training intensity during EET was relatively high in comparison with the intensity during GET, it still may have been too low due to the exercise limitation and poor physical fitness in the present patients Hypoxaemia during the exercise tests may also have limited exercise performance and may have concealed differences between groups Possibly, the effects of EET may be more pronounced in less disabled patients who can reach higher exercise intensities

In conclusion, pulmonary rehabilitation was safely applied in this group of patients with severe COPD, and improved exercise performance and quality of life EET in addition to GET did not result in an additional improvement in exercise performance, but induced physiologic training effects and improved gas exchange during exercise

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CHAPTER 8

Long-term effects of pulmonary rehabilitation in patients with COPD and hypoxaemia at peak exercise

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Submitted

8.1 Abstract

Study Objective – In this study we investigated the long-term effects of pulmonary rehabilitation in patients with COPD and exercise-induced hypoxaemia during a follow-up of 12 months. Furthermore we compared the effects of oxygen-supplemented training and additional eccentric exercise training with general exercise training on room air.

Patients and methods – Thirty-six patients with COPD (age mean (SEM) 60 (2) yrs; FEV_1 1.2 (0.1) L) and exercise hypoxaemia (arterial oxygen saturation (SaO_2) < 90%) participated in an in-patient pulmonary rehabilitation programme (10 weeks, 5 days/week). They were randomly allocated to general exercise training while breathing room air (GET/RA), GET while breathing supplemental oxygen (GET/O_2) or eccentric exercise training in addition to GET/RA (GET/EET). Pulmonary function, exercise performance and quality of life were measured before and after pulmonary rehabilitation, and at 3, 6 and 12 months during follow-up. The number of exacerbations and pulmonary care utilization during 12 months preceding pulmonary rehabilitation were compared with those during follow-up.

Results – Pulmonary rehabilitation significantly increased maximal work load during incremental cycle exercise (Wmax) in the GET/RA and the GET/EET group. Six min walking distance (6MWD) and other daily life activities (stair-climbing, weight-lifting), and quality of life scores increased in all groups. Breathing supplemental oxygen and additional eccentric exercise training did not add to the effects of training on room air. During follow-up the overall gains diminished by approximately 40% in all groups. When all three groups were taken together, Wmax (7 (3) W), 6MWD (66 (16) m), stair-climbing, weight-lifting exercise, and quality of life (CRDQ score: 14 (3) points) remained significantly increased above baseline after 12 months ($p<0.01$). Pulmonary function did not change, but resting PaO_2 showed a significant decrease after 12 months (0.8 kPa; $p<0.01$). The number of exacerbations treated at home was increased during follow-up (1.3 (0.2) versus 0.6 (0.2), $p=0.001$), while the number of visits to the out-patient clinic and hospitalization days did not change.

Conclusions – In all three training groups clinically relevant improvements were observed in exercise performance and quality of life. Supplemental oxygen and eccentric exercise training did not add to the effects of training on room air. The effects of pulmonary rehabilitation diminished, but benefits of the the treatment were maintained during 12 months of follow-up.

8.2 Introduction

In patients with COPD, hypoxaemia during exercise may contribute to the reduced exercise tolerance Exercise-induced hypoxaemia is caused by hypoventilation, diffusion-perfusion limitation and a low mixed venous PO_2 (low cardiac output) [1] Supplemental oxygen relieves hypoxaemia and has acute beneficial effects on exercise performance [2,3] Recent guidelines recommend the use of supplemental oxygen during exercise training in patients with exercise-induced hypoxaemia [3,4] However, the short-term and long-term effects of training have not yet been fully established in these patients

Many studies have shown that pulmonary rehabilitation may improve exercise performance and quality of life in patients with COPD Although the effects tended to diminish during follow-up, improvements were maintained up to 24 months [5-11] These studies included patients with moderate to severe COPD A small number of patients were hypoxaemic at rest or during exercise and received supplemental oxygen during the training The results in this subgroup were not analysed separately [7-10] Oxygen-supplemented exercise training has shown to increase exercise performance in patients with COPD, but no comparison was made with a control training group breathing room air [12,13]

Dynamic exercise can be accomplished either by concentric (positive work) or eccentric muscle contractions (negative work) During eccentric exercise (e g lowering a weight) the contracting muscle lengthens in a controlled way, whereas during concentric exercise (e g lifting a weight) the muscle shortens [14] Eccentric contractions are associated with a low oxygen cost and ventilatory requirement [14-16] In a previous study we found a reduction of 30% in VE and VO_2 during eccentric cycle exercise testing in comparison with concentric exercise at given constant work loads up to 50% of maximum in patients with COPD [17] The effects of eccentric exercise training have not been studied before in patients with COPD We hypothesized, that in patients with a limited ventilatory reserve and a reduced oxygen uptake capacity due to a diffusion-perfusion limitation, eccentric exercise might be a useful component of an exercise training programme

The aim of the present study was to investigate the long-term effects of a 10-week comprehensive pulmonary rehabilitation programme on exercise performance and quality of life in this selected group of patients with severe COPD and exercise-induced hypoxaemia We compared the effects of oxygen supplemented-exercise training and additional eccentric leg exercise training with general exercise training on room air Pulmonary function, exercise capacity, quality of life and health care utilization were studied during a follow-up period of 12 months

8.3 Methods

Patients

A prospective study was undertaken in 36 patients with stable COPD[18]. All patients were referred to our hospital for pulmonary rehabilitation. They met the following inclusion criteria: hypoxaemia (arterial oxygen saturation (SaO_2) < 90%) at maximum exercise, and an increase in the alveolar-arterial difference in oxygen tension ($P(A\text{-}a)O_2$) of at least 2 kPa from rest to maximum exercise during maximal incremental cycle exercise. Patients were excluded if they had a resting PaO_2 of less than 8.5 kPa, a mean nocturnal SaO_2 of less than 90%, a mean pulmonary artery pressure (MPAP) of more than 25 mmHg measured at rest by Doppler echocardiography[19], and if they had neuromuscular or cardiovascular disease.

All patients were ex-smokers Their medication was not changed during the study Exacerbations were treated with corticosteroids and antibiotics if needed. They were familiar with the procedures of exercise testing. Informed consent was obtained from each patient. The study was approved by the hospital ethics committee.

Pulmonary rehabilitation programme

All patients participated in a multidisciplinary in-patient programme for 10 weeks, 5 days/week, which consisted of physical training, breathing retraining, physical therapy (relaxation and mobilization exercises), education and psycho-social support At the start of the study the patients were randomly allocated to general exercise training (GET) while breathing room air (GET/RA), GET while breathing supplemental oxygen at a flow rate of 4 L/min through a dual-prong nasal cannula (GET/O_2), or to GET and additional eccentric exercise training (GET/FET) on an electrically-braked cycle ergometer (Lode, Groningen The Netherlands), which was adapted for negative work [20]. The training exercises have been described in detail in chapter 3, 6 and 7.

Follow-up

After completion of the pulmonary rehabilitation programme the patients were encouraged to continue exercises and activities of daily life at home. During a follow-up period of 12 months after completion of the rehabilitation programme the patients attended six supervised one-day training sessions similarly as during pulmonary rehabilitation. These meetings were held monthly during the first three months and at 6, 9 and 12 months

Outcome measures

Pulmonary function and exercise performance were tested before and after pulmonary rehabilitation and on separate occasions at 3, 6 and 12 months after the

follow-up sessions The patients had to be in a stable condition for at least three weeks

Pulmonary function tests
Spirometry and transfer coefficient for carbon monoxide (KCO, single breath) were performed according to European Respiratory Society (ERS) standards [21] Maximal inspiratory esophageal pressure ($PI_{es\ max}$) in sitting position was measured with a pressure transducer (Validyne, Northridge, California) during sniff manoeuvres from residual volume [22] Doppler echocardiography was repeated at the end of the rehabilitation programme, but not during follow-up

Maximal incremental exercise test
The patients cycled concentrically on an electrically-braked cycle ergometer (Lode, Groningen, The Netherlands) at a pedalling rate of 60 RPM, breathing room air The work rate was increased each minute by 10% of the estimated maximal work load (Wmax), until exhaustion [23] Arterial blood samples were drawn from an indwelling catheter in the brachial artery Minute ventilation (VE), oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured every 30 s by a mixing chamber ergospirometry unit (Oxycon IV, Mijnhardt, Maarsen, The Netherlands) Breathlessness at peak exercise was scored on a modified Borg scale [24] Peak VE was related to predicted maximal exercise values (VEmax predicted= 37 5 x FEV_1) [25]

Activities of daily life
After 3 practise tests, the 6 min walking distance (6MWD) was measured in a gymnasium[26], while standardized encouragement was given [27]

Stair-climbing was performed on an exercise staircase with a hand-rail, which had 4 steps for going up, a plateau, and 3 steps for going down The number of rounds during 5 min of exercise were counted

During weight-lifting the patients held a weight of 2 kg in the predominant hand and moved it between racks at 20 cm above and below shoulder level The number of lifts to both levels during 3 min was counted [28]

Quality of life
Quality of life was assessed by means of the Chronic Respiratory Disease Questionnaire (CRDQ) [29] The test was administered at the start of the study, 6 weeks after completion of the pulmonary rehabilitation programme, and at 6 and 12 months of follow-up

Clinical course and pulmonary care utilization
The number of visits to the out-patient clinic, the number of exacerbations treated at home and disease related hospitalization days during 12 months preceding

pulmonary rehabilitation and during 12 months of follow-up were obtained from the medical records.

Statistical analysis

The data were analysed with the Statistical Analysis System (SAS) package (SAS Institute Inc., Cary, NC, USA). The results were expressed as mean (SEM). The effects of pulmonary rehabilitation within the different training groups were analysed with the Wilcoxon test for paired samples. Differences between the groups were tested with the Kruskal Wallis test (Chi-square approximation). Significance was accepted at a p-value less than 0.05. The Wilcoxon test for paired samples was also used to compare the data at 4 time points during follow-up with those at baseline for all three groups together. Since multiple comparisons were performed, the level of significance for each test was set at $\alpha' = 2\alpha/k$ (i.e. $p<0.025$), where α is the overall level of significance and k the number of comparisons. Due to the interdependency of the tests α' is likely to be closer to α.

8.4 Results

Patients and pulmonary function

The patients had moderate to severe airway obstruction with signs of emphysema as suggested by hyperinflation and a reduced transfer coefficient for carbon monoxide. At the start of the study FEV_1 in the GET/O_2 group (0.9 (0.1) L) was significant lower than in the GET/EET group (1.4 (0.1) L; p=0.02). Resting PaO_2 and $PaCO_2$ were normal, but $P(A\text{-}a)O_2$ was elevated in all groups (Table 8.1).

All patients completed the pulmonary rehabilitation programme. During the follow-up period 8 patients dropped out of the study (22%). Two patients died due to respiratory insufficiency (1 in the GET/O_2 and 1 in the GET/EET group), 4 patients could not accomplish the tests because respiratory function deteriorated (1 in the GET/RA and 3 in the GET/O_2 group), 1 patient in the GET/RA group developed a non-pulmonary malignancy and 1 patient in the GET/EET group withdrew for social reasons. Another 4 patients in the GET/RA, 2 in the GET/O_2 and 3 in the GET/EET group could not complete the tests at 3 or 6 months during the follow-up period due to an exacerbation.

Pulmonary rehabilitation had no effect on MPAP. At the end of follow-up resting $P(A\text{-}a)O_2$ showed a further increase in the GET/EET group of 1.3 (0.3) kPa ($p<0.01$) (Table 8.1). After pulmonary rehabilitation and at the end of follow-up the differences in these indices between groups were not significant.

Cycle exercise intensity during the training

During the last 6 weeks of interval cycle exercise training the GET/RA, the GET/O_2 and the GET/EET group were able to train at a work rate of 114 (9)%,

Table 8.1 Anthropometrics and resting pulmonary function

	GET/RA			GET/O_2			GET/EET		
	baseline	after P.R.	12 mo follow-up	baseline	after P.R.	12 mo follow-up	baseline	after P.R.	12 mo follow-up
Patients, *n*	12	12	10	12	12	8	12	12	10
Sex, *M/F*	10/2	10/2	8/2	10/2	10/2	7/1	10/2	10/2	9/1
Age, *yrs*	59±4	-	61±3	63±1	-	64±2	59±3	-	59±3
BMI, *kg/m²*	23.2±0.5	23.0±0.5	22 5±0.5	22.5±0.6	22.1±0.3	22.4±0.8	24.7±1.2	24.8±1.0	24.3±1.0
TLC %predicted, *%*	114±6	110±3	114±4	109±5	110±6	109±9	115±7	114±7	20±7
IVC %predicted, *%*	93±5	95±5	95±4	87±5	98±7*	94±8*	97±5	99±6	104±6
FEV_1, *L*	1.2±0.1	1.2±0.1	1 2±0 2	0.9±0.1#	1.0±0.1	1.1±0 2	1.4±0.1	1.4±0.1	1.4±0.2
FEV_1 %predicted, *%*	38±3	38±3	35±3	29±2#	33±3	34±5	45±4	44±3	42±4
KCO %predicted, *%*	37±4	40±4	40±5	30±4	30±4	28±6	41±5	40±16	34±5
$Pt_{es\,max}$, *kPa*	8.0±0.8	8.6±0.8	7.9±0 6	6.2±0.4	6 8±0.4	7.6±0 6	6.7±0.6	7.0±0.4	8.0±0.6
MPAP, *mmHg*	13±0.9	16±7	-	17±2	15±1	-	15±1	16±1	-
PaO_2, *kPa*	10.5±0.3	10.2±0.4	9.9±0.4	10 2±0.5	9 5±0.6	10.3±0.5	10.4±0.4	10.6±0.4	9.4±0.3
$PaCO_2$, *kPa*	5.0±0.2	4.9±0.2	5 3±0 2	5.1±0 3	5 3±0.3	5.2±0 4	5 0±0.2	4.9±0.1	4.8±0.2
$P(A\text{-}a)O_2$, *kPa*	4.4±0.3	5.2±0.5	4.8±0.3	4.6±0 6	5 5±0.4	4.8±0.5	4 4±0.4	4.9±0.4	5.7±0 4*

Values are presented as mean ± SEM. GET· general exercise training/room air; GET/O_2: general exercise training/supplemental oxygen; GET/EET: general exercise training/eccentric exercise training; BMI: body mass index; TLC: total lung capacity (He-dilution); IVC: inspiratory vital capacity, FEV_1: forced expiratory volume in one second; KCO· transfer coefficient for carbon monoxide (single-breath), $Pt_{es\,max}$: maximal inspiratory oesophageal pressure; MPAP: mean pulmonary artery pressure; PaO_2: arterial oxygen tension; $PaCO_2$: arterial carbon dioxide tension; $P(A\text{-}a)O_2$: alveolar-arterial difference in oxygen tension.

*$p<0.05$: change from baseline within group.

#$p<0.05$: comparison between GET/O_2 and GET/EET.

124 (12)% and 106 (7) of Wmax, respectively (p=0.12). During eccentric exercise the patients in the GET/EET group were able to continue cycling for 15 min at a work rate of 160 (20) % of concentric maximum.

Maximal incremental cycle exercise

Before training, the responses to maximal incremental cycle exercise were similar in all groups (Table 8 2) Peak VE approached or exceeded predicted maximal exercise values. The increase in $PaCO_2$ by 0 4 to 0 8 kPa did not differ significantly between groups. PaO_2 decreased and $P(A\text{-}a)O_2$ increased by approximately 3 kPa in all groups. Base excess decreased during exercise (Δbase excess) between 4 8 and 6.3 mmol/L (range 1 to 10 mmol/L).

Pulmonary rehabilitation significantly increased Wmax in the GET/RA group by 17 (4) W and in the GET/EET group by 10 (3) W, but not in the GET/O_2 group (7 (7) W; p=NS). In the GET/EET group heart rate at peak exercise was lower than before training (120 (3) versus 124 (4) beats/min, $p<0.05$). In all groups peak VE and VO_2 and Δbase excess did not change. PaO_2 at peak exercise after training was lower than before in the GET/RA group (6.9 (0.2) versus 7.3 (0.2) kPa, $p<0.05$) and in the GET/O_2 group (6.7 (0.3) versus 7.2 (0.3) kPa; $p<0.05$). Dyspnoea scores at maximum tended to decrease in all groups, but these changes did not reach significance.

At the end of follow-up, Wmax in the GET/RA was still increased by 10 (4) W ($p<0.05$), while the other variables did not differ from baseline in all groups. At that time point differences between groups were not significant

Activities of daily life and quality of life

Pulmonary rehabilitation significantly increased 6MWD by 123 (22) m in the GET/RA group, by 86 (22) m in the GET/O_2 group and by 118 (19) m in GET/EET group. At the end of follow-up the change in 6MWD from baseline was 92 (33) m in the GET/RA group ($p<0$ 05), 37 (31) m in the GET/O_2 group (p=NS) and 64 (22) m in the GET/EET group ($p<0.05$) (Table 8.3)

The performance during stair-climbing and weight-lifting increased significantly by 20 to 40% in all groups after pulmonary rehabilitation. The largest improvement was achieved in the GET/RA group, which was sustained during follow-up (Table 8.3).

At the start of the study, the CRDQ score was significant lower in the GET/EET group (68 (7) points) than in the GET/RA group (85 (5) points; p=0.04) (Table 8.3). Pulmonary rehabilitation increased the total CRDQ score by 15 (2) points in the GET/RA group, by 19 (4) points in the GET/O_2 group and by 16 (3) points in the GET/EET group ($p<0.01$). Increases in CRDQ score were maintained during follow-up in the GET/RA and the GET/EET group

The effects of pulmonary rehabilitation on daily life activities and quality of life did not differ significantly between groups.

Table 8.2 Maximal incremental cycle exercise testing

	GET/RA			GET/O_2			GET/EET		
	baseline	after P.R.	12 mo follow-up	baseline	after P R.	12 mo follow-up	baseline	after P.R.	12 mo follow-up
Wmax, *W*	70±15	87±17**	80±16*	58±10	65±11	72±11	75±12	85±14*	87±14
Heart rate, *beats/min*	133±6	132±7	136±6	126±5	126±5	128±7	124±4	120±3*	128±5
VE, *L/min*	43±6	43±6	41±7	35±4	37±7	38±	46±3	46±3	48±4
VE %VEmax pred., *%*	96±7	95±5	97±4	101±7	92±4	89±5	90±5	89±4	97±7
VO_2, *L/min*	1.2±0.1	1.2±0.2	1.2±0 2	1.0±0.1	1.0±0.1	1 0±0 1	1.3±0 1	1.3±0.1	1.3±0.1
O_2 pulse, *ml O_2/beat*	8.7±0.7	9.3±0.9	8.5±0.8	8.3±0.7	8.4±0.6	8.0±0.8	10.4±0.8	11.4±0.7	10.6±1.1
PaO_2, *kPa*	7 3±0.2	6.9±0.2*	7.2±0.3	7.2±0.3	6.7±0.3*	7.1±0.4	7.7±0.1	7 9±0 3#	7.9±0.3
$PaCO_2$, *kPa*	5.7±0.3	5.7±0.2	5.8±0 3	5.9±0.4	5.8±0.4	5 9±0.6	5.4±0.3	5.5±0 3	5.4±0.3
Δbase excess, *mmol/L*	-5 3±0.8	-5.7±0.8	-6 4±0.8	-4.8±1.0	-5.4±1 0	-6 6±1 0	-6.2±0.8	-5.4±0.7	-6.0±0.8
$P(A\text{-}a)O_2$, *kPa*	7.7±0 4	8.2±0.4	7.9±0.4	7.4±0.4	8.1±0 4	7 8±0.7	7.9±0 3	7.4±0.4	7.8±0.3
Dyspnoea, *Borg scale*	7.3±0.7	5 8±0.6	6.2±0 6	6.6±0.6	5.3±0.4	7.0±0.6	7.3±0.7	5.8±0 6	5.7±0.5

Values are presented as mean ± SEM. Wmax: maximum work load; $\dot{V}E$: minute ventilation; VO_2: oxygen consumption; Δbase excess: change in base excess. For further definitions see legend to Table 8.1.

*p<0.05; **p<0.01: change from baseline within group.

#p<0.05: GET/EET compared to GET/RA and GET/O_2

Table 8 3 Activities of daily life and quality of life

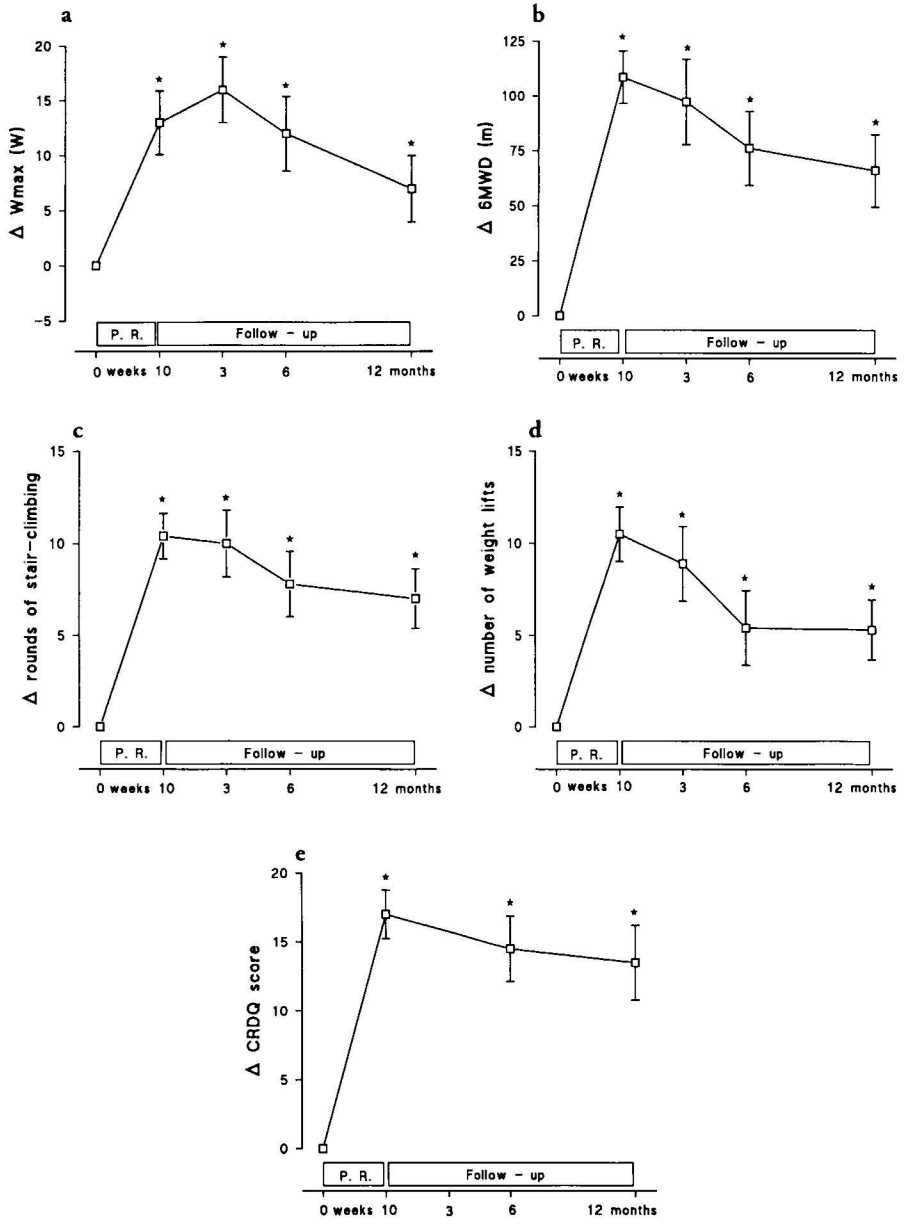
	GET/RA			GET/O_2			GET/EET		
	baseline	after P R	12 mo follow-up	baseline	after P R	12 mo follow-up	baseline	after P R	12 mo follow-up
6MWD, *m*	487±55	610±48**	594±55*	389±40	475±52**	478±50	445±41	563±37**	536±43*
Stair-climbing, *n*	29±3	41±5**	39±6*	22±3	30±4**	31±4	27±3	38±4**	35±4
Weight-lifting, *n*	36±4	52±5**	44±4*	37±3	46±2**	42±4	33±3	40±3*	38±4
CRDQ score	85±5	100±5**	96±4*	79±5	98±5**	93±9	68±7§	84±5**	84±7**

Values are presented as mean ± SEM 6MWD 6 min walking distance For exercise testing protocols for stair-climbing and weight-lifting see text
CRDQ chronic respiratory disease questionnaire
*p<0 05, **p<0 01 change from baseline within group
§p<0 05 comparison between GET/EET and GET/RA

Table 8 4 Exacerbations and pulmonary care utilization before pulmonary rehabilitation and during follow-up

	GET/RA (n=12)		GET/O_2 (n=12)		GET/EET (n=12)		All groups (n=36)	
	12 mo before P R	follow-up after P R	12 mo before P R	follow-up after P R	12 mo before P R	follow-up after P R	12 mo before P R	follow-up after P R
Time of follow-up, *mo*		11 8±0 2		11 5±0 5		11 8±0 2		11 8±0 1
Out-patient clinic visits, *n*	4 1±0 6	3 0±0 5	2 8±0 3	3 0±0 6	3 5±0 8	2 9±0 6	3 5±0 3	3 0±0 3
Exacerbations treated at home, *n*	0 8±0 4	1 2±0 4	0 4±0 2	1 7±0 4*	0 7±0 3	1 1±0 3	0 6±0 2	1 3±0 2*
Hospitalization, *days*	12±3	7±3	14±4	13±6	14±5	14±7	13±2	11±3

Values are presented as mean ± SEM
*p<0 01 change from baseline within group
No significant differences were present between groups



Figures 8.1a,b,c,d,e The mean change in maximal exercise capacity during incremental cycle exercise (ΔWmax; 8.1a), in 6 min walking distance (Δ6MWD; 8.1b), in performance during stair-climbing (Δ rounds of stair-climbing; 8.1c) and weight-lifting (Δ number of weight-lifts; 8.1d), and in CRDQ score (Δ CRDQ score; 8.1e) after pulmonary rehabilitation (P.R.) and during 12 months for the three training groups together (GET/RA, GET/O_2 and GET/EET: before and after pulmonary rehabilitation n=36, at 3 months n=22, at 6 months n=26, at 12 months n=28). Error bars represent SEM.
*$p<0.01$: change from baseline within group.

Follow-up in the three training groups together

The effects of training on exercise performance did not differ between groups, and the number of subjects was reduced during follow-up due to drop-outs. Therefore the data were analysed for the 3 training groups together. At 3 months 22 patients, at 6 months 26 patients and at 12 months 28 patients could be evaluated. The measurements at the different time points during follow-up were compared with baseline.

At the end of follow up, resting PaO_2 was lower (9.8 (0.2) versus 10.4 (0.3) kPa; $p<0.01$), and $P(A\text{-}a)O_2$ was higher (5.1 (0.2) versus 4.5 (0.3) kPa; $p<0.01$) in comparison with baseline.

Pulmonary rehabilitation increased Wmax by 13 (3) W. During follow up Wmax decreased, but was still 7 (3) W above baseline level after 12 months ($p<0.01$) (Figure 8.1a). 6MWD increased by 109 (12) m during pulmonary rehabilitation and was 66 (16) m above baseline at 12 months ($p<0.01$) (Figure 8.1b). The number of rounds during stair-climbing improved by 10 (1) during training, and was 7 (2) rounds above baseline at 12 months ($p<0.01$) (Figure 8.1c). The increases in the number of weight-lifts were 11 (2) and 5 (2) ($p<0.01$), respectively (Figure 8.1d). Quality of life scores increased by 17 (2) points during pulmonary rehabilitation, and were 14 (3) points above baseline at 12 months ($p<0.01$) (Figure 8.1e).

Clinical course and pulmonary care utilization

Information was available of all 36 patients. The follow-up was less than 12 months in one patient of the GET/RA group (10 months), one of the GET/O_2 group (6 months) and one of the GET/EET group (10 months). The number of exacerbations treated at home were higher during follow-up, which was significant in the GET/O_2 group [1.7 (0.4) versus 0.4 (0.2), $p<0.01$)]. The number of visits to the out-patient clinic and hospitalization days did not change after pulmonary rehabilitation in the 3 groups (Table 8.4). Similar results were found when all 3 groups were taken together, the number of exacerbations being significantly higher during follow-up (1.3 (0.2) versus 0.6 (0.2), $p=0.001$).

8.5 Discussion

This study showed that pulmonary rehabilitation improved exercise performance and quality of life in patients with COPD who are hypoxaemic during exercise. Training with supplemental oxygen and additional eccentric exercise training did not result in a further improvement as compared to training on room air. In the GET/EET group the improvement in Wmax was accompanied with a reduced cardiac response and improved gas exchange. Changes in these indices, however, did not differ between groups. For the three groups together, the overall gains

diminished by approximately 40% during a follow-up period of 12 months, but remained significantly elevated above baseline

This is the first study describing the effects of training in patients with COPD and exercise-induced hypoxaemia The diffusion capacity below 50% of predicted[30], the elevated $P(A\text{-}a)O_2$ at rest and the increase in $P(A\text{-}a)O_2$ by more than 3 kPa during exercise[31] indicate that a diffusion-perfusion limitation rather than hypoventilation was the cause of the hypoxaemia during exercise in our patients [1 31] Therefore we believe, that the lower FEV_1 in the GET/O_2 group did not influence the effects of training in our study Moreover, $PaCO_2$ during maximal incremental exercise increased similarly in all groups, indicating equal impairment of the ventilatory pump

In patients with COPD, hypoxaemia contributes to the acute increase in the pulmonary artery pressure during exercise, the long-term effects of which are unknown [33] Sergeysels et al [12] reported a small but significant increase in PaO_2 and decrease in $PaCO_2$ of 1 kPa or less, and a decrease in MPAP from 17 to 13 mmHg after 6 months of training In other studies, changes in pulmonary function and gas exchange after training and during follow-up were also small or absent [7 9 11 34] In our study, SaO_2 during the training was kept above 90% in all training groups Training did not affect resting MPAP During follow-up lung function remained unchanged Although resting PaO_2 was somewhat lower after 12 months, gas exchange during exercise did not worsen Thus we conclude that exercise training can be safely applied in this selected group of patients with COPD

Effects of supplemental oxygen and eccentric exercise training

We were interested in training modalities which might yield extra improvements during pulmonary rehabilitation In this study, we focussed on oxygen-supplemented training and additional eccentric exercise training We did not include an untreated control group, since these severely disabled patients can not be denied therapy for as long as one year We found that supplemental oxygen during the training did not add to the effects of GET Recently, similar results have been reported in patients who did not desaturate during exercise [35] Several factors may account for the absence of an additional effect of training with supplemental oxygen Firstly, the GET/O_2 group did not achieve higher work rates during cycle exercise training than the GET/RA group (124% versus 110% of Wmax) The training regimen consisted of interval training and short bouts of exercise Endurance exercise was not performed during the training Thus, the GET/RA group could keep SaO_2 above 90% at relatively high work rates Secondly, supplemental oxygen abolishes the hypoxaemia and reduces lactate levels during exercise, which also might have reduced the training stimulus in our patients [2 36] Finally, oxygen utilization by the peripheral muscle is impaired due to deconditioning [37 38] Thus the limiting factor for exercise capacity may not be the oxygen delivery to the working muscles, but the oxygen uptake and utilization in these muscles

In the GET/EET group, parameters of cardiocirculatory fitness improved The heart rate at Wmax was reduced after training, suggesting a physiologic training effect This may be caused by the higher amount of work performed during training compared to the other groups and to the increased muscular tension during eccentric muscle contractions [39] This training effect had disappeared three months later Thus, in all groups the increases in exercise performance were mainly achieved by improved muscular efficiency

Long-term effects of pulmonary rehabilitation

Beneficial long-term effects of pulmonary rehabilitation have been previously reported in patients with COPD, although not particularly in those desaturating during exercise.[5 7 12] In a recent study by Ries et al [10] in 119 patients with COPD (FEV_1 1 2 L) an 8-week pulmonary rehabilitation programme increased maximum workload and endurance during treadmill exercise in comparison with an education programme, which were preserved 12 and 24 months, respectively Other studies have reported similar results for endurance treadmill exercise and for 12MWD [5 7 8 34] After 24 weeks of supervised training 6MWD increased by 38 m in comparison with a control group [3]

The favourable effects of pulmonary rehabilitation in our patients are consistent with reports showing that pulmonary function, oxygen requirement and arterial blood gas levels were not related to 6MWD, and improvement in 12MWD during training [40 41] Furthermore, the in-patient pulmonary rehabilitation programme and the frequency of the training sessions (10 weeks, 5 days/week) may have contributed to our results as well In the studies mentioned above, the patients trained as in- or out-patients 1 to 3 times per week for 6 to 8 weeks [7 10 12] Rehabilitation at home has shown to improve quality of life, but not Wmax during cycle exercise or 6MWD over 18 months, whereas Wmax and 6MWD decreased in the control group [11]

The increases in CRDQ in our study are in the same range as have been reported by others In the study by Vale et al. pulmonary rehabilitation increased quality of life scores (CRDQ) by 24 points, 8% of which was lost after 11 months [8] In other studies the increase in CRDQ from baseline to the end of the follow-up which was about 10 points higher in the treatment group than in the control group.[9 11] In contrast, in the study by Ries et al.[10] measures of depression and general quality of life did not change

In our study, the number of exacerbations treated at home was higher during follow-up than during 12 months preceding pulmonary rehabilitation, possibly because the patients recognized symptoms at an earlier stage. This was not accompanied by an increase in visits to the out-patient clinic, indicating improved coping with the disease However, this did not lead to a reduction in hospitalization days. This was in part explained by 6 patients, who accounted for 65% of the hospital stay during follow-up. In the study by Ries et al.[10] pulmonary rehabilitation tended

to diminish hospital stay, but this was not significant. So, although pulmonary rehabilitation may not reduce hospitalization related medical costs, pulmonary care will be more efficacious afterwards, thus contributing to the improved functional capacity and quality of life.

In our study, the decline in exercise performance and quality of life during follow-up was more pronounced in comparison with other reports. This may be explained by a more impaired respiratory function and lower exercise performance at baseline. In the study by Vale et al.[8] lower baseline values for 12MWD were related to a greater decline during follow-up.

The number of drop-outs in our study was in the same range as has been reported by others.[8,9,11] However, dropping out or suffering from prolonged exacerbations was not related to lower gains in Wmax, 6MWD or daily life activities during pulmonary rehabilitation. Thus, patients with severe COPD and a poor performance should not be excluded from pulmonary rehabilitation.

It is unclear whether a higher frequency of sessions during the follow-up might have improved our results. In the study by Vale et al.[8], patients who participated a maintenance programme did not do better during follow-up than patients who did not. In a study by Wijkstra et al.[11], once weekly sessions were not superior to sessions which were held once monthly.

Clinical implications and conclusions

In conclusion, pulmonary rehabilitation may result in considerable gains in exercise performance and quality of life in patients with COPD and exercise-induced hypoxaemia. Oxygen-supplemented exercise training and additional eccentric exercise training were not superior to GET on room air, while keeping SaO_2 above 90%. However, eccentric exercise training may induce an improvement in cardiocirculatory fitness. Effects of pulmonary rehabilitation sustained over 12 months.

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CHAPTER 9

Summary and conclusions

9.1 Introduction

Many studies have shown beneficial effects of pulmonary rehabilitation in patients with COPD This study focussed on the effects of pulmonary rehabilitation in patients with severe COPD who are hypoxaemic at peak exercise due to a limitation in oxygen-uptake capacity In these patients, the use of supplemental oxygen during the training is recommended, but the effects have not yet been studied in comparison with a control group breathing room air Alternatively, the low ventilatory requirement and metabolic cost of eccentric exercise in healthy subjects may make this type of exercise suitable especially for training of these patients Eccentric exercise has never been applied in patients with COPD Therefore we investigated the short- and long-term effects of oxygen-supplemented exercise training, and the effects of additional eccentric exercise training in comparison with a general exercise training regimen on room air, during an in-patient pulmonary rehabilitation programme

9.2 Summary

In *chapter 1* the exercise limiting factors in patients with COPD are discussed An overview is given of the effects of pulmonary rehabilitation and exercise training in COPD Oxygen therapy and eccentric exercise as potential components of training in severe COPD are reviewed and the aims of the study are outlined

Patients with severe COPD may have difficulty in performing daily life activities In these patients, constant work load exercise even at low work rates might result in a maximum exercise response In *chapter 2* the ventilatory response to maximal incremental exercise and to exercise at various submaximal constant work loads was investigated in 15 subjects with COPD (mean (SD) FFV_1 1 1 (0 4) L) All subjects performed a maximal incremental exercise test (MIT) and four single stage exercise tests (SST) on a cycle ergometer at 60% (SST60%), 45% (SST45%), 30% (SST30%) and 15% (SST15%) of maximal work capacity (Wmax) A ventilatory steady-state, defined as an increase in VE of less than 10% during at least 3 consecutive minutes after the first 4 min of exercise, was achieved in only 6 subjects during SST60%, in 10 subjects during SST45% and in 11 subjects during SST30% Three subjects still did not reach a steady-state during SST15% The work load and oxygen consumption (VO_2) at the anaerobic threshold (AT), as approximated by the V-slope method during MIT, corresponded with the highest achievable steady-state work load and VO_2 in 4 and 6 subjects, respectively All 6 subjects in whom Wmax and peak VO_2 exceeded 75 W and 1 L/min, respectively, reached a steady-state at SST45% In the other 9 subjects, the exercise response to single stage exercise could not be predicted by physiologic variables

of impairment at rest, or by parameters of MIT. It was concluded, that in patients with severe COPD the ventilatory response to exercise at submaximal work loads varies widely and should be determined individually. In some patients exercise at low and moderate constant work loads may increase ventilation up to maximum levels in a similar way as during maximal incremental exercise. As a result, a wide range in measurements of endurance exercise capacity might be expected, as cycling time and walking distance, as well as in the effects of training on these indices. Therefore, we developed tests, which more specifically quantified performance during daily life activities of lower and upper extremities, like stair-climbing and unsupported weight-lifting.

The effect of physical training on functional capacity mainly depends on the intensity at which exercise is performed However, patients with severe COPD do not tolerate high levels of exercise due to breathlessness In *chapter 3* the intensity of our general exercise training programme, as it is carried out during in-patient pulmonary rehabilitation (10 weeks, 5 days per week), was investigated in 13 patients with severe COPD. During the training the exercise intensity was increased as tolerated by the patients. The intensity was assessed by heart rate (HR) and dyspnoea ratings (score on a modified Borg scale) measured during one training session (duration 80 (7) min). HR and Borg scores were compared with peak HR and Borg score obtained during a maximal incremental cycle exercise test at the start of the study The ventilatory load during the training was estimated by the relationship between HR and VE during the initial incremental cycle exercise test. The HR during various exercises of the training programme varied between 94 and 103% of peak HR. Borg scores varied between 2.0 and 5.7, and were lower than the Borg score at peak exercise (6 5 (2.0)). HR was more than 90% of peak HR during 36 (33) min of the whole training session, which corresponded with a VE of 81 (11) % of peak VE The maximal incremental exercise test was repeated at the end of the programme Training significantly increased Wmax from 62 (25) to 73 (21) W. Since aerobic capacity did not improve (peak VO_2 before and after training 1.1 (0 19) L/min) the increase in maximum exercise performance was explained by an improvement in exercise efficiency (Wmax/peak VO_2 63 (11) versus 55 (18) W/(L/min); p=0.1) and adaptation to dyspnoea. It was concluded, that patients with severe COPD are able to train at high individual levels of exercise, and that training improved maximal exercise performance. Hence, our training programme was appropriate and could be used to evaluate the effects of additional training modalities.

In healthy subjects, oxygen consumption and cardiorespiratory responses are lower during eccentric exercise (negative work, Wneg) than during concentric exercise (positive work, Wpos) at the same work load. In *chapter 4* the ventilatory response to Wneg was investigated in 12 patients with COPD (FEV_1 1.5 (0.4) L, 46 (16)

% of predicted) VE, VO_2 and VCO_2 were 30% lower during Wneg than during Wpos at constant work loads of 25% and 50% of the individual maximal (positive) work capacity (Wmax) The breathing reserve during 25%Wneg was 11 (8) % and during 50%Wneg 18 (14) % higher than during Wpos at corresponding work loads ($p<0.01$) VE/VO_2 and VE/VCO_2 were similar during Wpos and Wneg $PaCO_2$ increased by 0.1 (0.4) kPa during 50%Wneg and by 0.7 (0.5) kPa during 50%Wpos ($p<0.01$) It was concluded that, similar to normal subjects, the ventilatory requirements of Wneg were considerably lower than those of Wpos at the same external work load Thus, eccentric exercise may be a convenient type of exercise and training especially in patients who have a limited ventilatory reserve and oxygen uptake capacity

The close temporal relationship between arterial plasma potassium levels ($[K^+]a$) and minute ventilation (VE) during exercise, as described by others in healthy subjects, suggests that potassium may contribute to the exercise hyperpnoea In *chapter 5* this relationship was investigated during the same experiment as described in chapter 4 During exercise at a constant work load of 50% of Wmax, VE closely mirrored VCO_2 during Wpos and Wneg As a result the slope of the relationship between VCO_2 and VE was similar during both types of exercise (median 27.8 versus 32.1) VE also closely correlated with $[K^+]a$, but the slope of the relationship between $[K^+]a$ and VE was steeper during Wpos than during Wneg (39.1 versus 18.3 (9.1) L min^{-1} mM^{-1}, $p=0.012$) Thus, for a given increase in $[K^+]a$ the increase in VE was significantly less during Wneg It was concluded, that in patients with COPD potassium did not explain the reduced exercise ventilation during Wneg Although potassium may act as a ventilatory drive also in patients with COPD, the magnitude of the effect on ventilation during exercise at moderate work loads is negligible

Supplemental oxygen has *acute* beneficial effects on exercise performance in patients with COPD The mechanism by which this is achieved is complex The value of training with supplemental oxygen has still to be determined In chapter 4 we have already shown that the ventilatory requirement of eccentric exercise is reduced in patients with COPD, making this type of exercise a challenge to incorporate in a training regimen In *chapter 6,7 and 8* we investigated whether patients with severe COPD, who develop hypoxaemia during exhausting exercise due to a limitation in oxygen-uptake capacity, might benefit from supplemental oxygen or additional eccentric exercise during the training We hypothesized, that these two training modalities enable these patients to achieve higher exercise intensities, and may thus enhance the effects of training on room air To test this hypothesis we studied 36 patients with COPD (mean age (SD) 60 (9) yrs, FEV_1 1.2 (0.4) L) and a normal resting PaO_2, who developed hypoxaemia during maximal incremental cycle exercise (arterial oxygen saturation (SaO_2) < 90% at

peak exercise) All patients participated in an in-patient pulmonary rehabilitation programme (10 weeks, 5 days/week) They were randomly allocated to general exercise training while breathing room air (GET/RA group), to GET while breathing supplemental oxygen at a flow rate of 4 L/min through a dual-prong nasal cannula (GET/O_2 group), or to eccentric cycle exercise training in addition to GET/RA (GET/EET) Table 9 1 shows the characteristics of the patients in the different training groups SaO_2 was not allowed to fall below 90% during the training in all groups The short- and long-term effects of the different training modalities on exercise performance and quality of life were compared The results are summarized in Table 9 2

Table 9 1 – Patient characteristics

	GET/RA	GET/O_2	GET/EET
Patients, *n*	12	12	12
Sex, *M/F*	10/2	10/2	10/2
Age, *yrs*	59±13	63±5	59±10
FEV_1, *L*	1 2±0 5	0 9±0 3#	1 4±0 4
FEV_1 %predicted, %	38±11	29±7#	45±13
KCO %predicted, %	37±14	30±14	41±17
PaO_2 at rest *kPa*	10 5±1 1	10 2±1 6	10 4±1 3
PaO_2 peak exercise, *kPa*	7 3±0 7	7 2±1 0	7 7±0 5

Values are presented as mean±SD GET/RA general exercise training/room air, GET/O_2 general exercise training/supplemental oxygen, GET/EET general exercise training/eccentric exercise training, FEV_1 forced expiratory volume in one second, KCO transfer coefficient for carbon monoxide (single-breath), PaO_2 arterial oxygen tension, $PaCO_2$ arterial carbon dioxide tension

#p<0 05, ##p<0 01 comparison between GET/O_2 and GET/EET

In *chapter 6* the effects of oxygen-supplemented exercise training were compared with the effects of training room air To study the acute effects of oxygen on exercise performance, exercise tests were both performed on air and 4 L/min oxygen Maximal exercise capacity (Wmax) and exercise efficiency (Wmax/peak VO_2) during maximal incremental cycle exercise on room air increased significantly in the GET/RA group, but not in the GET/O_2 group Cycling time during single-stage exercise at 65% of maximum work load did not improve significantly in both groups Six min walking distance (6MWD), stair-climbing, and weight-lifting exercise, all while breathing room air, as well as quality of life scores (Chronic Respiratory Disease Questionnaire, CRDQ) increased significantly in both groups.

Table 9 2 Changes in exercise performance and quality of life after pulmonary rehabilitation and at 12 months of follow-up

	GET/RA		GET/O_2		GET/EET	
	P R	follow-up	P R	follow-up	P R	follow-up
Patients, *n*	12	10	12	8	12	10
Sex, *M/F*	10/2	8/2	10/2	7/1	10/2	9/1
ΔWmax, *W*	17±15**	10±12*	7±25	5±25	10±12*	5±10
Δ6MWD, *m*	123±77**	92±103*	86±77**	37±87	118±66**	64±71*
ΔStair-climbing, *n*	12±8**	10±11*	8±7**	5±8	11±8**	6±7
ΔWeight-lifting, *n*	16±10**	8±8*	9±6**	2±12	7±8*	5±7
ΔCRDQ score	15±7**	11±10*	19±14**	12±22	16±11**	17±12**

Values are presented as mean±SD Wmax maximum work load during maximal incremental cycle exercise, 6MWD 6 min walking distance, CRDQ Chronic Respiratory Disease Questionnaire

*p<0 05, **p<0 01 change from baseline within group

No significant differences were present between groups

Supplemental oxygen had acute beneficial effects on exercise performance before and after training, the largest effect being observed in cycling time Training significantly increased Wmax, peak VCO_2 and 6MWD while breathing oxygen in both groups The acute effects of oxygen and the effects of training did not differ between the GET/RA and the GET/O_2 group This lack in difference between both groups was attributed to various factors The acute effects of oxygen varied between patients and were not related to arterial blood gases. Hence, not all patients could benefit from supplemental oxygen during the training Indeed, the GET/O_2 group did not achieve higher intensities during interval cycle exercise as compared to the GET/RA group Furthermore, breathing oxygen may have reduced the production of lactate, which is an important determinant of the training stimulus. Finally, a diffusion limitation at the level of the deconditioned skeletal muscles may have been present in our patients, thus impeding muscle oxygen utilization, in spite of an increased oxygen supply by breathing oxygen

In *chapter 7* the effects of additional eccentric exercise training were compared with the effects of general exercise training Training exercises and exercise tests were performed on room air. During eccentric exercise training the patients were able to cycle continuously for 15 min at an intensity of 160 (69) % of Wmax achieved during maximal incremental exercise at the start of the study without being distressed by dyspnoea or hypoxia In contrast, the work load achieved during five two-minute bouts of concentric cycling, spaced with two-minute intervals of rest, in the GET group and in the GET/EET group was 114 (32) and 106 (23)% of Wmax, respectively In spite of the higher exercise intensity and

total amount of work in the GET/EET group, training similarly improved maximum work load (Wmax), 6MWD, stair-climbing, weight-lifting and quality of life, in both groups However, beneficial changes in the physiologic response to exercise were observed only in the GET/EET group Training significantly decreased heart rate at rest (10 beats/min) and peak heart rate at Wmax (4 beats/min) in the GET/EET group, but not in the GET group (decrease 5 and 1 beats/min, respectively) The increase in alveolar-arterial difference in oxygen tension $P(A\text{-}a)O_2$ during incremental cycle exercise was also less after training in the GET/EET group, whereas no change was observed in the GET group The creatinine height index as measure of peripheral muscle mass increased by 8% in both groups, but this was significant only in the GET/EET group These results suggest that eccentric exercise induces a physiologic training effect in terms of an improved cardiocirculatory response to exercise and possibly an increased peripheral muscle mass in patients with severe COPD

In *chapter 8* the long-term effects of pulmonary rehabilitation in all three training groups were investigated during a follow-up of 12 months after completion of the programme Tests of pulmonary function, exercise performance on room air and quality of life, as performed before and after pulmonary rehabilitation, were repeated at 3, 6 and 12 months during follow-up In addition, the number of exacerbations and pulmonary care utilization during 12 months preceding pulmonary rehabilitation were compared with those during follow-up During follow-up 8/36 patients dropped out of the study (22%) Therefore, follow-up analysis was performed for all groups together Of the overall gains from pulmonary rehabilitation 60% remained at the end of follow-up Wmax (mean (SEM) 7 (3) W), 6MWD (66 (16) m), stair-climbing, weight-lifting exercise, and quality of life (CRDQ score 14 (3) points) were still significantly increased above baseline after 12 months Pulmonary function did not change The number of exacerbations treated at home was significantly higher during follow-up (1 3 (0 2) versus 0 6 (0 2), while the number of visits to the out-patient clinic and hospitalization days did not change Education and improved coping with the disease may have contributed to early detection of exacerbations by the patients, and thus to the long-term benefits of pulmonary rehabilitation We conclude that in all three training groups clinically relevant improvements in exercise performance and quality of life were maintained during 12 months of follow-up

9.3 Conclusions, general discussion and directions for future research

The following conclusion can be drawn from the results presented in this study

- In patients with severe COPD, the ventilatory response to exercise at various constant work loads varies widely, and has to be determined individually As a result, large differences in exercise performance exist between subjects

- Patients with severe COPD can achieve high exercise intensities during the training as compared to the individual's maximum exercise capacity.
- In patients with COPD the ventilatory requirement and metabolic cost of eccentric exercise are 30% lower than those of concentric exercise at similar work loads up to 50% of maximum.
- The lower exercise ventilation during eccentric exercise is not explained by an equivalent decrease in plasma potassium levels.
- In patients with severe COPD, who are hypoxaemic at peak exercise due to a limitation in oxygen uptake capacity, pulmonary rehabilitation including physical training improved exercise performance and quality of life.
- Supplemental oxygen and eccentric exercise training did not add to the effects of general exercise training on room air.
- Eccentric exercise training improved cardiocirculatory fitness in terms of a decrease in heart rate at rest and at maximum exercise, and may possibly increase peripheral muscle mass.
- Clinically relevant effects of pulmonary rehabilitation were maintained during 12 months of follow-up.

Comparing the three training groups, exercise performance and the effects of training tended to be lower in the GET/O2 group. Since airway mechanics is an important determinant of exercise limitation, one might question whether this was caused by the lower FEV_1 in the GET/O_2 group. Figure 9.1 shows the relationship between FEV_1 and the changes in maximum work load after training (ΔWmax) in the different training groups. No significant correlation was found between Wmax and FEV_1 (r= 0.24, p=0.16), indicating that the gain in Wmax did not

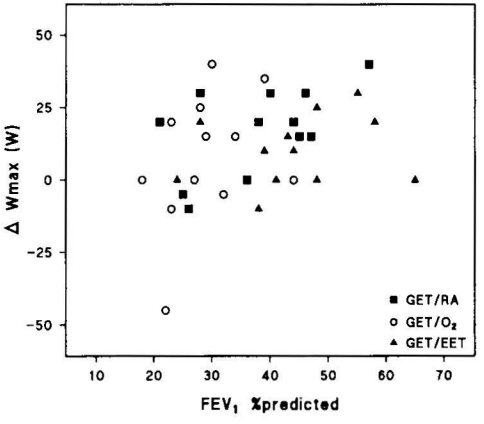


Figure 9.1 The relationship is shown between FEV_1 %predicted and the change in maximum work load during maximal incremental cycle exercise after training (ΔWmax) in the three training groups.

depend on FEV_1. Furthermore, $PaCO_2$ as a determinant of ventilatory pump failure, showed the same increases during maximal incremental exercise in all groups Thus, differences in exercise performance and effects of training were unlikely to be due to differences in performance of the ventilatory pump.

This study in patients with severe COPD showed that exercise tolerance and the effects of training varied widely between subjects in all groups. The effects of training could not be predicted by lung function parameters, arterial blood gases at rest and during exercise, or acute effects of oxygen on exercise performance. This is caused by the complex mechanism of exercise limitation in which mechanical properties of the lungs, pulmonary haemodynamics, oxygen-uptake capacity of the lungs, cardiac function, nutritional state as well as ventilatory and peripheral muscle function may all play a role Future studies should focus on the assessment of these potentially exercise limiting factors and the development of specific training modalities In patients with COPD, little information is available on pulmonary haemodynamics, and right and left ventricular function as factors limiting exercise tolerance and whether these can be influenced by training. Recently, peripheral muscles in COPD have shown to contribute to the exercise limitation, as their function may be impaired. Diffusion limitation and impaired metabolism may be present Possibly, oxidative stress may influence the performance of exercising muscles The value of isolated muscle training and ergonomics in severe COPD has still to be determined. Answers to these questions may help to identify patients who are suitable candidates for exercise training and to select the most appropriate training programme in individual patients.

In these severely disabled patients the main purpose of pulmonary rehabilitation is to increase functional capacity in a way that activities of daily life can be performed with less effort and breathlessness However, adequate measurement of functional capacity is difficult. This study showed that exercise at various constant work loads resulted in a maximum exercise response in some patients, whereas others reached a ventilatory steady-state and could continue exercise. Thus, maximal and submaximal exercise tests on a cycle ergometer or on a treadmill may not reflect simple daily tasks in individual patients In the present study, we therefore tried to quantify some daily activities of lower and upper extremities such as stair-climbing and unsupported weight-lifting. Further studies should provide information on the cardiocirculatory and ventilatory load as well as the subjective response to various daily tasks in these patients. Furthermore, studies should focus on the reproducibility and sensitivity of exercise tests, which assess performance during activities related to the patients' individual goals of treatment.

CHAPTER 10

Samenvatting en conclusies

10.1 Introductie

Meerdere studies hebben aangetoond, dat patienten met een chronisch obstructieve longaandoening (chronic obstructive pulmonary disease, COPD) baat hebben bij longrevalidatie. Deze studie richt zich op de effecten van longrevalidatie bij patienten met COPD, die tijdens een maximale inspanning hypoxisch worden als gevolg van een beperkte zuurstof-opnamecapaciteit. Er wordt geadviseerd om aan deze patienten extra zuurstof toe te dienen tijdens de training, hoewel de effecten hiervan nog niet zijn vergeleken met de effecten van training in een controlegroep, die kamerlucht ademt In plaats van extra zuurstof kan inspanning met excentrische spiercontracties (negatieve arbeid) een geschikte trainingsvorm zijn voor deze patienten, omdat deze vorm van inspanning gekenmerkt wordt door een lage zuurstofconsumptie en ventilatoire belasting. Negatieve arbeid is nog niet eerder toegepast bij patienten met COPD In deze studie onderzochten wij of het gebruik van extra zuurstof tijdens de training of additionele training met excentrische spiercontracties, betere resultaten zou geven dan het algemeen trainingsprogramma, waarbij kamerlucht werd geademd Daartoe werden de effecten van longrevalidatie, waar deze trainingsvormen een onderdeel van uitmaakten, op korte en lange termijn geevalueerd.

Specifieke vraagstellingen binnen dit onderzoek waren·

- Hoe is de ventilatoire respons tijdens inspanning met verschillende sub-maximale constante belastingen bij patienten met een ernstig COPD? (Hoofdstuk 2)
- Met welke intensiteit trainen patienten met een ernstig COPD tijdens een algemeen trainingsprogramma? (Hoofdstuk 3)
- Hoe groot is bij patienten met COPD de metabole en ventilatoire belasting tijdens excentrische spiercontracties (negatieve arbeid) in vergelijking met concentrische contracties (positieve arbeid) met dezelfde uitwendige belasting? (Hoofdstuk 4)
- Kunnen verschillen in plasma kalium concentraties de verschillen in inspanningshyperpnoe tussen negatieve en positieve arbeid bij patienten met COPD verklaren? (Hoofdstuk 5)
- Wat zijn de effecten van training *met* en *zonder* gebruik van extra zuurstof, als onderdeel van longrevalidatie, op het prestatievermogen en de kwaliteit van leven bij patienten met een ernstig COPD, die hypoxisch worden tijdens maximale inspanning op basis van diffusie-perfusie problematiek? (Hoofdstuk 6)
- Wat zijn de effecten van additionele training met negatieve arbeid bij deze groep van patienten? (Hoofdstuk 7)
- Wat zijn de effecten van longrevalidatie op langere termijn (1 jaar) bij deze groep van patienten? (Hoofdstuk 8)

10.2 Samenvatting

In *hoofdstuk 1* worden de factoren besproken, die een rol spelen in de beperking van de inspanningstolerantie bij patiënten met COPD. Vervolgens wordt de waarde van longrevalidatie en van fysieke training bij patiënten met COPD besproken. Zuurstof-therapie en excentrische spiercontracties als behandelopties bij patiënten met een ernstig COPD, worden belicht aan de hand van gegevens uit de literatuur. Tenslotte worden de doelen van dit onderzoek geformuleerd.

Veel patiënten met een ernstig COPD hebben al moeite met het uitvoeren van dagelijkse activiteiten. Sub-maximale belastingen kunnen bij hen resulteren in een maximale ventilatoire respons als de inspanning wordt gecontinueerd. In *hoofdstuk 2* wordt de ventilatoire respons tijdens inspanning met opklimmende belasting tot maximum, en tijdens inspanning met verschillende sub-maximale constante belastingen beschreven in 15 patiënten met COPD (gemiddelde (SD) FEV_1 1.1 (0.4) L). Alle patiënten verrichtten een maximale inspanningstest op de fietsergometer met opklimmende belasting tot uitputting (maximal incremental exercise test, MIT), en 4 inspanningstesten met een constante belasting (single stage exercise test, SST) van 60% (SST60%), 45% (SST45%), 30% (SST30%) en 15% (SST15%) van het maximum (Wmax). Een ventilatoire steady-state tijdens inspanning werd gedefinieerd als een stijging van VE van minder dan 10% gedurende ten minste 3 minuten, na de eerste 4 minuten van inspanning. Deze werd bereikt door 6 patiënten tijdens SST60%, 10 patiënten tijdens SST45% en 11 tijdens SST30%. Drie patiënten bereikten zelfs tijdens SST15% geen steady-state. De anaerobe drempel tijdens MIT werd berekend met behulp van de V-slope methode. Deze voorspelde de hoogste belasting en zuurstof consumptie ($\dot{V}O_2$) waarbij nog een steady-state werd bereikt in respectievelijk 4 en 6 patiënten. Alle patiënten met een Wmax van meer dan 75 Watt en een piek $\dot{V}O_2$ van meer dan 1 L/min bereikten een steady-state tijdens SST45%. Bij de overige 9 patiënten kon de ventilatoire respons tijdens SST niet worden voorspeld op basis van longfunctie, bloedgassen en gegevens verkregen tijdens MIT. De conclusie was, dat de ventilatoire respons tijdens SST een grote variatie vertoonde en individueel moet worden vastgelegd. Tijdens inspanning met een geringe belasting kan de ventilatie tot maximale waarden stijgen, overeenkomend met de hoogste ventilatie bereikt tijdens een maximale inspanningstest. Dit betekent dat een grote variatie mag worden verwacht in de prestaties tijdens testen, die het duurvermogen op de fiets, of de 6 minuten loopafstand meten. Ook de effecten van training op deze parameters zullen variëren. Bovendien is het de vraag of deze testen representatief zijn voor activiteiten van het dagelijkse leven. Daarom hebben wij voor deze studie twee nieuwe testen ontwikkeld, om specifiek het prestatievermogen tijdens enkele veelvoorkomende activiteiten te quantificeren. Wij hebben daarbij gekozen voor een oefening van de onderste en van de bovenste extremiteiten, namelijk trap lopen en het plaatsen van een halter in een rek.

Het effect van fysieke training op het prestatievermogen hangt voornamelijk af van de trainingsintensiteit. De belastbaarheid van patienten met een ernstig COPD is echter laag, als gevolg van de dyspnoe die optreedt tijdens inspanning. In *hoofdstuk 3* onderzochten wij de intensiteit van ons trainingsprogramma, zoals uitgevoerd tijdens klinische longrevalidatie (10 weken, 5 dagen/week), bij 13 patienten met een ernstig COPD Tijdens de oefeningen werd gestreefd naar de hoogste belasting, die qua dyspnoe werd verdragen. De trainingsintensiteit werd bepaald aan de hand van de hartfrequenties (heart rate, HR) en dyspnoe scores (Borg), die voor elke patient tijdens 1 sessie (duur 80 (7) min) werden gemeten. HR en Borg scores werden vergeleken met de piek HR en Borg scores tijdens een maximale inspanningstest op de fietsergometer, die aan het begin van de revalidatie was verricht De ventilatoire belasting tijdens de training werd geschat met behulp van de relatie tussen HR en VE tijdens de maximale inspanningstest. Tijdens de verschillende oefeningen van het trainingsprogramma bedroeg de HR 94-104% van de piek HR. De Borg scores lagen tussen 2 0 en 5.7, en waren lager dan de Borg score tijdens de maximale inspanningstest (6 5 (2.0)). Gedurende 36 (33) min van de gehele duur van de sessie bedroeg de HR meer dan 90% van piek HR, hetgeen overeenkomt met een VE van 81 (11) % van de piek VE De maximale inspanningstest werd aan het einde van de revalidatie herhaald. Wmax verbeterde significant van 62 (25) naar 73 (21) Watt Omdat de aerobe capaciteit niet toenam (de piek VO_2 was voor en na training 1 1 L/min), werd de verbetering van de inspanningscapaciteit toegeschreven aan een toegenomen efficientie (Wmax/piek VO_2 63 (11) versus 55 (18) Watt/(L/min); p=0.1) en aan adaptatie aan de dyspnoesensatie. De conclusie was, dat patienten met een ernstig COPD werden getraind op een hoog individueel niveau en dat training de maximale belastbaarheid verbeterde. Tijdens longrevalidatie wordt daarmee een adequaat trainingsprogramma geboden, welk geschikt is om de waarde van aanvullende trainingsmodaliteiten te testen.

Voor gezonde proefpersonen geldt dat de zuurstofconsumptie en daarmee de cardiale en ventilatoire respons tijdens inspanning met dynamisch excentrische spiercontracties (negatieve arbeid, Wneg) lager zijn dan tijdens dynamisch concentrische spiercontracties (positieve arbeid, Wpos) bij dezelfde uitwendige belasting. In *hoofdstuk 4* vergeleken wij de ventilatoire respons tijdens Wneg met die tijdens Wpos bij 12 patienten met COPD (FEV_1 1 5 (0.4) L, 46 (16) % van voorspeld) In vergelijking met Wpos waren de VE, VO_2 and VCO_2 tijdens Wneg 30% lager bij een identieke constante belasting, overeenkomend met 25% en 50% van het individuele maximum tijdens positieve arbeid (Wmax). De ventilatoire reserve, gedefinieerd als $VE/(FEV_1 \times 37.5) \times 100\%$, was tijdens 25%Wneg en 50%Wneg respectievelijk 11 (8) % en 18 (14) % hoger dan tijdens Wpos voor dezelfde belasting ($p<0.01$) Er werden geen verschillen gevonden in VE/VO_2 en in VE/VCO_2 tussen Wpos en Wneg. De $PaCO_2$ steeg met 0.1 (0.4) kPa tijdens 50%Wneg en met 0 7 (0.5) kPa tijdens 50%Wpos ($p<0.01$). De bevindingen kwamen overeen met die bij ge-

zonden. Door de veel lagere metabole en ventilatoire belasting tijdens Wneg lijkt negatieve arbeid een aantrekkelijke vorm van inspanning voor patiënten met COPD, in het bijzonder voor patiënten met een beperkte ventilatoire reserve en zuurstof-opnamecapaciteit.

De regulatie van de ventilatie tijdens inspanning is complex. Kalium wordt wel beschouwd als één van de factoren, die in belangrijke mate kan bijdragen aan de inspanningshyperpnoe. Dit is afgeleid uit het nauwe verband dat bij gezonden tijdens inspanning is gevonden tussen de arteriële plasma kalium concentratie ($[K^+]a$) en het ademminuutvolume ($\dot{V}E$). *Hoofdstuk 5* beschrijft deze relatie voor patiënten met COPD tijdens hetzelfde experiment als vermeld in hoofdstuk 4. Tijdens Wpos en Wneg met een constante belasting van 50% van Wmax werd een nauw en identiek verband gevonden tussen $\dot{V}E$ en $\dot{V}CO_2$. De helling van de relatie tussen $\dot{V}CO_2$ en $\dot{V}E$ was respectievelijk 31.2 (8.8) en 29.0 (5.7). Er werd ook een significant verband gevonden tussen $\dot{V}E$ en $[K^+]a$, maar de helling was veel steiler tijdens Wpos dan tijdens Wneg (42.7 (21.6) versus 18.7 (9.1) L min^{-1} mM^{-1}; p=0.012). Met andere woorden, voor dezelfde stijging van $[K^+]a$ was de toename van de $\dot{V}E$ significant minder tijdens Wneg. Dit betekent, dat bij patiënten met COPD, kalium de lagere ventilatoire respons tijdens Wneg niet kan verklaren. De bijdrage die kalium levert aan de inspanningshyperpnoe bij deze patiënten lijkt verwaarloosbaar.

Het toedienen van extra zuurstof aan patiënten met COPD geeft een *acute* verbetering van het prestatievermogen. Het mechanisme, dat hieraan ten grondslag ligt is complex. Het is nog niet duidelijk of het gebruik van extra zuurstof tijdens de training zinvol is. In hoofdstuk 4 werd reeds beschreven, dat training door middel van excentrische spiercontracties (negatieve arbeid, Wneg) aantrekkelijk kan zijn voor patiënten met COPD, vanwege de lage ventilatoire belasting. In de *hoofdstukken 6,7 en 8* worden de effecten beschreven van training met extra zuurstof en van training met Wneg bij patiënten met een ernstig COPD, die hypoxisch worden tijdens maximale inspanning. De hypothese was, dat extra zuurstof of Wneg deze patiënten in staat stelt een hogere intensiteit tijdens de training te bereiken, waardoor een grotere trainingsprikkel wordt verkregen en een groter effect op het prestatievermogen in vergelijking met een algemeen trainingsprogramma, waarbij kamerlucht wordt geademd. Om deze hypothese te testen onderzochten we 36 patiënten met COPD (gemiddelde leeftijd (SD) 60 (9) jr; FEV_1 1.2 (0.4) L) en een normale PaO_2 in rust, die hypoxisch werden tijdens een maximale inspanningstest op de fietsergometer (O_2 saturatie, SaO_2 < 90% op het maximum) op basis van een beperkte zuurstof-opnamecapaciteit door diffusie-perfusie problematiek. Alle patiënten namen deel aan klinische longrevalidatie (10 weken, 5 dagen/week). De patiënten werden at random ingedeeld in drie groepen: een algemeen trainingsprogramma, waarbij kamerlucht werd geademd (General Exercise Training while breathing Room Air, GET/RA group), of GET met extra zuurstof, toegediend door een neusbril

met een flow van 4 L/min (GET/O_2 group), of GET/RA waaraan toegevoegd Wneg, uitgevoerd op een fietsergometer (Eccentric Exercise Training in addition to GET/RA, GET/EET). Tabel 10.1 vermeldt de gegevens van de patienten. Voor alle groepen gold, dat de SaO_2 tijdens de training niet lager mocht zijn dan 90%. De korte en lange termijneffecten op het prestatievermogen en op de kwaliteit van leven werden vergeleken. De belangrijkste resultaten staan vermeld in Tabel 10 2

Tabel 10 1 Gegevens van patienten

	GET/RA	GET/O_2	GET/EET
Patienten, *n*	12	12	12
Sexe, *man/vrouw*	10/2	10/2	10/2
Leeftijd, *jr*	59±13	63±5	59±10
FEV_1, *L*	1 2±0 5	0 9±0 3#	1 4±0 4
FEV_1 %voorspeld, *%*	38±11	29±7#	45±13
KCO %voorspeld, *%*	37±14	30±14	41±17
PaO_2 in rust, *kPa*	10 5±1 1	10 2±1 6	10 4±1 3
PaO_2 maximum, *kPa*	7 3±0 7	7 2±1 0	7 7±0 5

Waarden zijn weergegeven als gemiddelde ± SD GET/RA general exercise training/room air, GET/O_2 general exercise training/supplemental oxygen, GET/EET general exercise training/ eccentric exercise training, FEV_1 geforceerd expiratoir volume in een seconde, KCO transfer coefficient voor koolmonoxyde (single-breath), PaO_2 arteriele zuurstofspanning, $PaCO_2$ arteriele kooldioxydespanning
#p<0 05, ##p<0 01 GET/O_2 versus GET/EET

Tabel 10 2 Veranderingen in prestatievermogen en kwaliteit van leven na longrevalidatie en na 12 maanden follow-up

	GET/RA		GET/O_2		GET/EET	
	LR	follow-up	LR	follow-up	LR	follow-up
Patienten, *n*	12	10	12	8	12	10
Sexe, *man/vrouw*	10/2	8/2	10/2	7/1	10/2	9/1
ΔWmax, *Watt*	17±15**	10±12*	7±25	5±25	10±12*	5±10
Δ6MWD, *m*	123±77**	92±103*	86±77**	37±87	118±66**	64±71*
Δtrap lopen, *n*	12±8**	10±11*	8±7**	5±8	11±8**	6±7
Δhalter plaatsen, *n*	16±10**	8±8*	9±6**	2±12	7±8*	5±7
ΔCRDQ score	15±7**	11±10*	19±14**	12±22	16±11**	17±12**

Waarden zijn weergegeven als gemiddelde ± SD Wmax maximale belasting tijdens fietsergometrie, 6MWD 6 minuten loopafstand, CRDQ Chronic Respiratory Disease Questionnaire
*p<0 05, **p<0 01 verandering ten opzichte van de uitgangswaarde binnen de drie trainingsgroepen

In *hoofdstuk 6* worden de effecten van training met extra zuurstof beschreven. Om de *acute* effecten van zuurstof te bestuderen werden de fietstesten en de 6 minuten loopafstand (6 minute walking distance, 6MWD) uitgevoerd met (4 L/min) en zonder extra zuurstof. De maximale belasting (Wmax) en de efficiëntie (Wmax/piek $\dot{V}O_2$) tijdens de maximale inspanningstest op de fietsergometer zonder extra zuurstof verbeterde significant in de GET/RA groep, maar niet in de GET/O_2 groep. De tijd die patiënten konden fietsen tijdens een constante belasting van 65% van Wmax verbeterde in geen van beide groepen. 6MWD, trap lopen en het plaatsen van een halter in een rek, alle uitgevoerd zonder extra zuurstof, evenals de kwaliteit van leven (Chronic Respiratory Disease Questionnaire, CRDQ) verbeterden significant in beide groepen. Het ademen van extra zuurstof gaf een *acute* verbetering van het prestatievermogen zowel voor als na de training. Het grootste effect trad op in de fietstijd tijdens constante belasting. Voor wat betreft de testen uitgevoerd met extra zuurstof gaf training een significante verbetering van Wmax, piek $\dot{V}CO_2$ en 6MWD. De verschillen in de *acute* effecten van extra zuurstof en in de effecten van training tussen beide groepen waren niet significant. Het ontbreken van additionele trainingseffecten in de groep die trainde met extra zuurstof werd toegeschreven aan verschillende factoren. Het *acute* effect van extra zuurstof wisselde van patiënt tot patiënt en was niet gerelateerd aan arteriële bloedgaswaarden. Daardoor konden niet alle patiënten profiteren van het gebruik van extra zuurstof tijdens de training. Dit kwam tot uiting in de intensiteit bereikt tijdens interval training op de fiets, die inderdaad geen significant verschil liet zien tussen de GET/RA en de GET/O_2 groep. Het is ook mogelijk dat het ademen van extra zuurstof tijdens inspanning het moment van anaerobe verbranding uitstelt en daarmee de produktie van lactaat, dat wordt beschouwd als een belangrijke trainingsstimulus. Tenslotte kan bij patiënten met een ernstig COPD de diffusie van zuurstof op het niveau van de perifere spieren gelimiteerd zijn. Dit kan de opname en verbranding van zuurstof in de spier beperken, ondanks een toename in het aanbod van extra zuurstof via het respiratoire en cardiale systeem.

In *hoofdstuk 7* worden de effecten van training met excentrische spiercontracties beschreven. Tijdens training met Wneg waren de patiënten in staat om 15 min continu te fietsen met een belasting van 160% van Wmax, zoals gemeten aan de start van de studie tijdens een maximale inspanningstest op de fietsergometer. Tijdens dit onderdeel van de training traden weinig dyspnoeklachten op en bleef de SaO_2 boven 90%. Daarentegen was de belasting die werd bereikt tijdens interval training met concentrische spiercontracties als onderdeel van GET (5x 2 min fietsen afgewisseld met 2 min rust), in de GET/RA en in de GET/EET groep niet hoger dan respectievelijk 114 (32) en 106 (23) % van Wmax. De hogere intensiteit tijdens Wneg en de extra geleverde arbeid in de GET/EET groep kwamen niet tot uitdrukking in een extra verbetering van het prestatievermogen. In beide groepen werd een stijging waargenomen in Wmax, 6MWD, trap lopen, het plaatsen van een halter

in een rek en de kwaliteit van leven (CRDQ scores). De verschillen tussen de groepen waren niet significant. Wel werden alleen in de GET/EET groep fysiologische trainingseffecten gevonden Na de training was de HR in rust (10 slagen/min) en op maximum (4 slagen/min) significant lager dan voor de training. De afname in HR met respectievelijk 5 en 1 slagen/min in de GET/RA groep was niet significant De stijging van (A-a)PO_2 tijdens de maximale inspanningstest nam na de training significant af in de GET/EET groep, maar bleef onveranderd in de GET/RA groep. De creatinine hoogte index, die wordt gebruikt als maat voor de hoeveelheid perifere spiermassa, nam in beide groepen met 8% toe, welke stijging alleen significant was in de GET/EET groep. Deze resultaten geven aan, dat training waarvan negatieve arbeid een substantieel onderdeel uitmaakt, de cardio-circulatoire conditie van patienten met een ernstig COPD kan verbeteren en mogelijk een toename geeft van de perifere spiermassa

In *hoofdstuk 8* werden de lange-termijneffecten van longrevalidatie voor de drie trainingsgroepen onderzocht, tijdens een follow-up van 12 maanden na afloop van het programma. Longfunctieonderzoek, inspanningstesten (zonder extra zuurstof) en CRDQ scores werden afgenomen na 3, 6 en 12 maanden follow-up Het aantal exacerbaties, het aantal bezoeken aan de polikliniek en het aantal opname-dagen in het ziekenhuis 12 maanden voorafgaande aan longrevalidatie werden vergeleken met de aantallen tijdens de follow-up periode De uitval tijdens follow-up bedroeg 22% (8/36 patienten). Analyse van de gegevens werd daarom ook verricht voor de drie groepen samen. Gedurende de follow-up bleef 60% van de verbeteringen verkregen tijdens longrevalidatie behouden In vergelijking met de uitgangswaarden aan de start van de studie werd na 12 maanden follow-up een significante toename gevonden in Wmax (mean (SEM) 7 (3) Watt), 6MWD (66 (16) m), trap lopen, halter plaatsen in een rek en CRDQ scores (14 (3) punten). De longfunctie veranderde niet. Het aantal (thuis) behandelde exacerbaties was hoger tijdens follow-up (1.3 (0.2) versus 0 6 (0 2)), maar het aantal bezoeken aan de polikliniek en het aantal opname-dagen bleven onveranderd. Educatie en een verbeterde coping met de ziekte hebben mogelijk bijgedragen tot een toegenomen detectie van exacerbaties, en daarmee tot het consolideren van de effecten van revalidatie. De conclusie was dat ook 12 maanden na afloop van longrevalidatie nog klinisch relevante verbeteringen werden gevonden van het prestatievermogen en de kwaliteit van leven.

10.3 Conclusies, beschouwing en aanwijzingen voor verder onderzoek

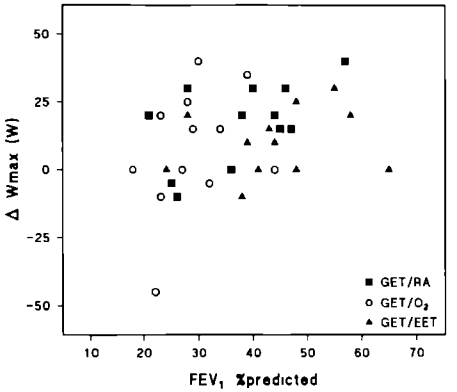
Op grond van de resultaten die gevonden zijn in deze studie kunnen de volgende conclusies worden getrokken.

- De ventilatoire respons tijdens inspanning met sub-maximale constante belastingen laat een grote variatie zien onder patienten met een ernstig COPD, en moet

individueel moet worden vastgelegd Dit verklaart mede de grote verschillen in de inspanningstolerantie, die bij deze patienten worden gevonden
- Patienten met een ernstig COPD zijn in staat om te trainen met een hoge intensiteit in relatie tot het individuele maximale niveau van inspanning
- De zuurstofconsumptie en de ventilatie bij patienten met COPD is tijdens negatieve arbeid 30% lager dan tijdens positieve arbeid voor identieke constante belastingen tot 50% van het individuele maximum tijdens positieve arbeid (Wmax)
- De afgenomen ventilatie tijdens negatieve arbeid kan niet worden verklaard uit een equivalente afname in de serum kalium concentratie
- Longrevalidatie, waar fysieke training onderdeel van uitmaakt, verbetert het prestatievermogen en de kwaliteit van leven bij patienten met een ernstig COPD, die hypoxisch worden tijdens maximale inspanning op basis van diffusie-perfusie problematiek
- Het toedienen van extra zuurstof tijdens de training, of additionele training met negatieve arbeid geeft geen extra verbetering van het prestatievermogen
- Additionele training met negatieve arbeid verbetert de cardio-circulatoire conditie in de zin van een afname in hartfrequentie in rust en tijdens maximale inspanning, en geeft mogelijk een toename van de perifere spiermassa
- Klinisch relevante effecten van longrevalidatie blijven ten minste 12 maanden na afloop van het programma aanwezig

Hoewel niet significant verschillend, waren de inspanningstolerantie en de effecten van training in de GET/O_2 groep minder dan in de GET/RA en de GET/EET groep Overwogen moet worden of deze verschillen zijn veroorzaakt door de lagere FEV_1 in de GET/O_2 groep, omdat de ademmechanica een belangrijke rol kan spelen in de beperking van de inspanningstolerantie Daarom onderzochten wij het verband tussen de FEV_1 uitgedrukt als percentage van voorspeld en de verandering in Wmax na training (ΔWmax) (Figuur 10 1) Er werd geen significante correlatie gevonden ($r=0\ 24$, $p=0\ 16$) Dit betekent dat de FEV_1 de effecten van training op Wmax niet kan verklaren Uit de gelijke mate van stijging van de $PaCO_2$ tijdens maximale inspanning in alle drie de groepen, kan worden afgeleid, dat de patienten in alle groepen in dezelfde mate ventilatoir beperkt waren Ook andere factoren dan de FEV_1 moeten dus mede hebben bijgedragen aan de tegenvallende resultaten in de GET/O_2 groep

In de onderzochte groep van patienten met een ernstig COPD werden grote verschillen gevonden in het prestatievermogen en in de effecten van training Het effect van training kon niet worden voorspeld aan de hand van longfunctieonderzoek, arteriele bloedgassen in rust of tijdens inspanning, of acute effecten van extra zuurstof op het prestatievermogen Dit wordt verklaard door het complex mechanisme van de beperking tijdens inspanning, waarbij vele factoren een rol spelen, zoals de mechanische eigenschappen van de long, de pulmonale haemodynamica, de zuurstof-opname capaciteit van de longen, de cardiale functies, de voedingstoestand en de functie van de ademhalingsspieren en de perifere skeletspieren Verder



Figuur 10 1 Het verband tussen de FEV_1 uitgedrukt als percentage van voorspeld en de verandering in maximale belasting na training (ΔWmax) in de drie trainingsgroepen

onderzoek naar de invloed van de afzonderlijke factoren op de inspanningstolerantie biedt meer inzicht in de beperking tijdens inspanning bij individuele patiënten. Op basis hiervan kunnen specifieke trainingsmodaliteiten worden ontwikkeld en gericht worden toegepast. Zo is nog weinig bekend over de invloed van de pulmonale circulatie en de functie van de rechter en linker ventrikel op de inspanningstolerantie bij patiënten met COPD. Ook is onduidelijk of deze factoren kunnen worden beïnvloed door training. Recent onderzoek bij patiënten met COPD heeft aangetoond, dat de functie van de perifere spieren was afgenomen, waardoor deze een beperkende factor waren tijdens inspanning. Een beperkte diffusie, een afgenomen metabolisme voor zuurstof en oxidatieve stress op spierniveau zijn mogelijke oorzaken. De waarde van geïsoleerde spiertraining en ergonomie moet nog worden bewezen. Deze vormen van training zullen de beste resultaten geven bij geselecteerde patiënten, bij wie de behandeling nauw aansluit bij de individuele beperkingen.

Een belangrijk doel van longrevalidatie bij patienten met een ernstig COPD is het verbeteren van de functionele capaciteit, zodanig dat activiteiten van het dagelijkse leven minder moeite kosten en minder dyspnoe veroorzaken. Het meten van de functionele capaciteit is echter moeilijk. Inspanning met een lage constante belasting gaf bij een aantal patiënten uit onze studie een maximale ventilatoire respons, terwijl anderen een steady-state bereikten en inspanning langer konden volhouden. Het is daarom de vraag of bij individuele patiënten, maximale en submaximale inspanningstesten op de fietsergometer of op de loopband een goede weergave zijn van alledaagse activiteiten. Daarom hebben wij een aantal specifieke activiteiten van het dagelijkse leven getest. Verder onderzoek moet inzicht geven in de cardio-circulatoire, metabole en ventilatoire belasting en naar de subjectieve respons tijdens deze activiteiten. Het ontwikkelen van valide en sensitieve testen, die prestaties tijdens specifieke dagelijkse activiteiten meten, stelt ons beter in staat om te evalueren in hoeverre de individuele doelstellingen van de patient zijn bereikt.

Abbreviations

ATP:	Adenosine triphosphate
ATS:	American Thoracic Society
BMI:	Body mass index
COPD:	Chronic obstructive pulmonary disease
CRDQ:	Chronic respiratory disease questionnaire
ECG:	Electrocardiogram
EET:	Eccentric exercise training
EMG:	Electromyogram
ERS:	European Respiratory Society
FEV_1:	Forced expiratory volume in one second
FRC:	Functional residual capacity
GET.	General exercise training
HR:	Heart rate
IVC:	Inspiratory vital capacity
KCO:	Transfer coefficient for carbon monoxide (single-breath)
maxWpos:	Maximal positive work capacity
MIT:	Maximal incremental exercise test
MPAP:	Mean pulmonary artery pressure
$P(A\text{-}a)O_2$:	Alveolar-arterial difference in oxygen tension
$PaCO_2$:	Arterial carbon dioxide tension
PaO_2:	Arterial oxygen tension
$P_{I_{oes\ max}}$:	Maximal inspiratory esophageal pressure
PR:	Pulmonary rehabilitation
PVR:	Pulmonary vascular resistance
RPM:	Revolutions per minute
RV.	Right ventricle
RVEF:	Right ventricular ejection fraction,
SaO_2:	Arterial oxygen saturation
SAS:	Statistical Analysis System
SEM.	Standard error of the mean
SST:	Single-stage exercise test
TLC:	Total lung capacity
TTI:	Time tension index
VD/VT.	Dead space/tidal volume ratio
VCO_2:	Carbon dioxide production
VE:	Minute ventilation
VE/VCO_2:	Ventilatory euivalent for carbon dioxide
VE/VO_2:	Ventilatory equivalent for oygen
VO_2:	Oxygen consumption
VT:	Ventilatory threshold
Wmax:	Maximum work load
Wneg:	Negative work
Wpos:	Positive work

Curriculum vitae

De auteur van dit proefschrift werd geboren op 9 maart 1959 te Helmond. Na het behalen van het diploma Atheneum B aan het Carolus Borromeus College te Helmond in 1976, studeerde hij Geneeskunde aan de Katholieke Universiteit Nijmegen. Het artsexamen werd behaald in 1983 In de periode 1983 tot 1985 was hij werkzaam als assistent-geneeskundige niet in opleiding (AGNIO) in het Groot Ziekengasthuis (thans Bosch Medicentrum) te 's Hertogenbosch, in het Elisabeth Ziekenhuis te Tilburg en in het Universitair Longcentrum, Medisch Centrum Dekkerswald te Groesbeek In 1985 werd begonnen met de opleiding tot longarts op de afdeling interne geneekunde van het Elisabeth Ziekenhuis te Tilburg (hoofd: Dr. J H.M Lockefeer) Vanaf 1987 werd de opleiding voortgezet in het Universitair Longcentrum van het Academisch Ziekenhuis Nijmegen (hoofd Prof. Dr. C L A. van Herwaarden). Sinds 1991 is hij als longarts verbonden aan dit centrum

Hij is gehuwd met Noor Lemmens en is vader van Marc, Ilse en Pauline

Dankwoord

Longrevalidatie is een doorlopend proces, waarbij motivatie, het open staan voor anderen, reflectie, het zelf vorm en inhoud geven en het vermogen tot verandering en acceptatie, centraal staan Met een proefschrift is het niet anders Daarom kan promoveren als revalidatie worden gezien en wat mij betreft vice versa De inzet waarmee patienten, na een vaak moeilijke periode, aan de slag gaan met longrevalidatie, werkt inspirerend Het is dan ook een voorrecht om met hen zo intensief te mogen werken Ik hoop van harte, dat dit onderzoek een bijdrage heeft mogen leveren aan hun welzijn

Veel heb ik geleerd van Professor Dr Folgering, met name van zijn grondhouding vanwaaruit hij wetenschappelijk onderzoek benadert, telkens opnieuw worden de meest elementaire vragen gesteld Beste Hans, je bent bijzonder attent voor iedereen Zo moet je, om tijd voor mij te winnen, de klokken op je kamer regelmatig hebben stilgezet

De manier waarop Dr Richard Dekhuijzen een onderwerp belicht hangt ongetwijfeld samen met zijn keuze van het diafragma De scherptediepte van zijn commentaar werkt stimulerend, alleen de opmerkingen "goed" en "prima" behoeven een speciale optiek

Ik ben mij bewust, dat dit onderzoek voor Professor Dr Kees van Herwaarden in meerdere opzichten een exercitie betekende Niet alleen op het gebied van patientenzorg, onderwijs en onderzoek heb ik mogen profiteren van zijn didactische aanpak

Op de afdeling longrevalidatie heb ik ervaren hoe effectief het werken in teamverband kan zijn Elly Berkeljon, jij was de enige die in staat was om patienten vooruit te laten gaan, zelfs als zij achteruit gingen

De laboranten van de longfunctie en het personeel van de polikliniek gaven geen krimp bij het verzetten van de afspraken en het verzetten daarvan Kees Lamers en Andre Hijmans traden op als geduldige relatietherapeuten als de computer weer eens niet met mij wilde communiceren (en andersom) De beeldvorming van Rob in den Bosch is in ieder geval niet gestoord Constance Kregting kreeg heel wat tekst te verwerken, en nog veel meer

Theo de Boo en Wim Lemmens van de afdeling Medische Statistiek schiepen orde in de chaos van data en stonden altijd voor mij klaar

De kracht van de 'korte lijnen" in Dekkerswald is vooral te danken aan de persoonlijke invulling, bereidheid en betrokkenheid, die men op alle afdelingen aantreft Al geruime tijd doe ik hier mijn voordeel mee, niet in de laatste plaats tijdens dit onderzoek

Stellingen

behorende bij het proefschrift
Pulmonary rehabilitation in patients with severe chronic obstructive pulmonary disease

1. Een onderverdeling van COPD in 'licht', 'matig' en 'ernstig' alléén op basis van de FEV_1 is ontoereikend, omdat de ernst van het ziektebeeld wordt bepaald door een complex van pulmonale en niet-pulmonale factoren.

2 De hoogste constante belasting, die nog een reele meting van het duurvermogen oplevert, is bij de meerderheid van patienten met een ernstig COPD minder dan 60% van het maximale inspanningsvermogen

3. De relatief lage metabole en ventilatoire belasting van excentrische spiercontracties (negatieve arbeid) ten opzichte van concentrische spiercontracties (positieve arbeid) maakt deze vorm van inspanning aantrekkelijk voor patienten met COPD

4. Bij patienten met COPD is de bijdrage van de arteriele plasma kalium concentratie aan de toename in ventilatie tijdens inspanning te verwaarlozen

5. Het ademen van extra zuurstof tijdens de training door patienten met COPD, die hypoxisch worden tijdens inspanning, geeft geen extra trainingseffect in vergelijking met het ademen van kamerlucht.

6. Het grote effect van longrevalidatie in een astmacentrum op de functionele capaciteit en de kwaliteit van leven rechtvaardigt deze vorm van behandeling.

7. Het meedelen van de diagnose COPD moet worden beschouwd als een 'slecht nieuws gesprek'.

8 Mensen die blijven roken, hebben er te weinig van opgestoken

9. De letter van de wet sluit criminaliteit niet uit
Daarom moet de geest van de wet(gever) worden verruimd

10. Hellemonders skréve niet alleen zèlluf hullie eige geskiedenis, zij schilderen deze ook.

Malden, 21 oktober 1997 J.M. Rooyackers